Newborn Screening Quality Assurance Program

2002 TANDEM MASS SPECTROMETRY ANNUAL SUMMARY REPORT

Volume 2 March 2003

INTRODUCTION

The Centers for Disease Control and Prevention (CDC), in partnership with the Association of Public Health Laboratories (APHL), operates the Newborn Screening Quality Assurance Program (NSQAP) to help screening laboratories achieve excellence in technical proficiency and maintain confidence in their performance while processing large volumes of specimens daily. Our program continually strives to produce certified dried-blood-spot (DBS) materials for reference and quality control (QC) analysis, to improve the quality and scope of our services, and to provide immediate consultative assistance. Through interactive efforts with the program's participants, we aspire to meet their growing and changing needs. Tandem Mass Spectrometry is the newest and most comprehensive method for detecting more than 30 disorders. This report is an overview of the specimen preparation and reported results for the 2002 pilot Tandem Mass Spectrometry Proficiency Testing (PT) Program. Comments and suggestions on how we may better serve the newborn screening laboratories are always welcomed.

Contents

Newborn screening for detection of treatable, inherited metabolic diseases is a major public health responsibility consisting of six parts: education, screening, follow-up, diagnosis, management, and treatment. Effective screening of newborns using DBS specimens collected at birth, combined with follow-up diagnostic studies and treatment, helps prevent mental retardation and premature death. These blood specimens are routinely collected from more than 95% of all newborns in the United States. State public health laboratories and their associated laboratories screen DBS specimens for inborn errors of metabolism and other disorders that require intervention.

For more than 24 years, CDC has conducted research on materials development and assisted laboratories with both quality control (QC) and PT issues. The quality assurance (QA) services primarily support state laboratories performing newborn screening; however, privately owned and foreign laboratories can also be accepted into the voluntary program. Currently, the program provides QA services in the form of quarterly PT panels that include amino acids and acylcarnitines. Dried-blood-spot QC materials are presently available for amino acids, and DBS-QC materials for acylcarnitines may be available by July of 2003. Dried-blood-spot materials for QC and PT are certified for homogeneity, accuracy, stability, and performance for most methods.

Along with the quarterly PT panels, which use blind-coded DBS specimens, the PT program provides to each laboratory an independent external assessment report of its performance. PT specimen panels are shipped to the laboratories in January, April, July, and October of each year. The laboratories have a three-week deadline for submitting the data. A quarterly summary that reports the enrichment values along with a summary of participant

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
and the
Association of Public Health Laboratories

means and cutoffs is compiled and returned to participating laboratories. At the end of every year, the program publishes an annual report to summarize the assessment outcomes over the year and serve as a resource of accumulated information that could benefit all laboratories involved in newborn screening efforts. Quarter 4, 2002, was the first quarter that presumptive clinical assessments were reported for the amino acids; therefore, only these data will be summarized. A more comprehensive summary will be available in 2004 with the addition of the acylcarnitine assessment component.

TANDEM MASS SPECTROMETRY PROFICIENCY TESTING

In 2002, NSQAP operated a pilot PT program for laboratories performing newborn screening tests using DBS specimens by tandem mass spectrometry (MS/MS). MS/MS is the new technology being used to detect amino acid metabolic disorders, urea cycle disorders, fatty acid oxidation disorders, and organic acid metabolic disorders. During the year, the program distributed four five-specimen panels to 64 active participants in the MS/MS PT program. Of these 64 participants, 29 were domestic laboratories (Figure 1) and 35 were foreign laboratories from 14 countries around the world (Figure 2). Quarterly reports were prepared using results that had been received by the deadline date and then distributed to all participant laboratories. Late-results data were not used in the quarterly reports; however, late data are included in the statistics of this annual MS/MS report. This report summarizes newly calculated cutoff values for amino acids and acylcarnitines from data collected in 2002. It also summarizes the amino acid presumptive classifications data reported by active participants from Quarter 4, 2002, with reference to their prospective median and mean cutoff values. Presumptive classification assessments for amino acids were established for the Quarter 4, 2002, PT panel. The presumptive assessment classifications for acylcarnitines will begin with the Quarter 3, 2003, PT event after review by the Newborn Screening Quality Assurance Subcommittee (APHL).

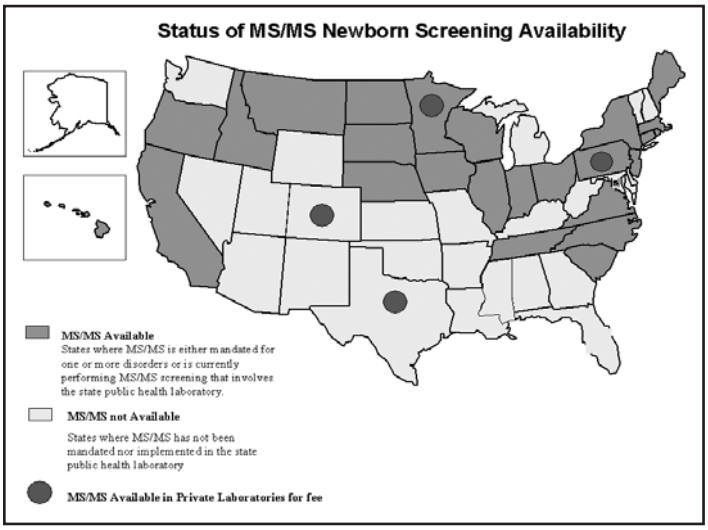

FIGURE 1. Twenty-nine laboratories in sixteen states participated in the NSQAP tandem mass spectrometry pilot PT program in 2002.

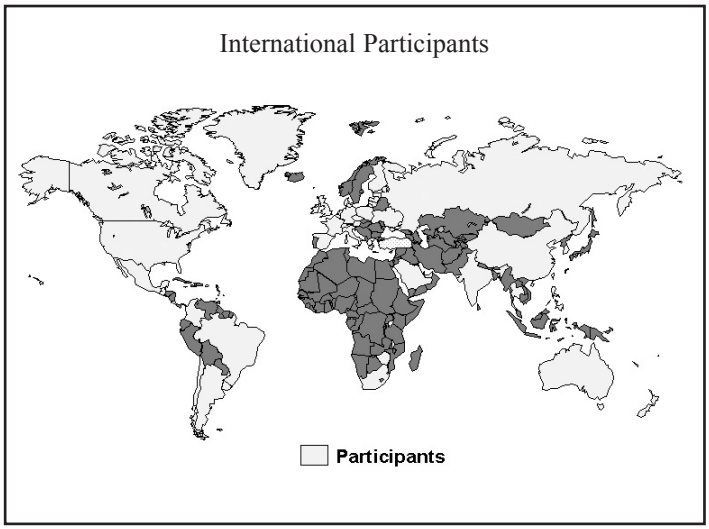

FIGURE 2. Worldwide participants including the foreign countries that participated in the NSQAP tandem mass spectrometry pilot PT program in 2002.

SPECIMEN PREPARATION

The amino acids and acylcarnitines PT panels distributed to participants in the 2002 PT program contain five blind-

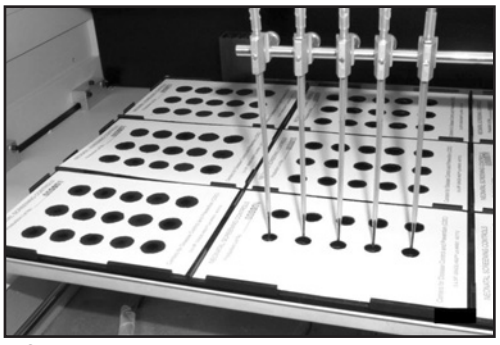

FIGURE 3. Automated blood spotting.

Program Information Web site:
http://www.cdc.gov/nceh/dls/newborn_screening.htm

coded DBS specimens containing either 75 µL or 100 µL of whole blood. The whole blood specimens were derived from two sources: blood with a 55% hematocrit of lysed red cells, or blood with a 55% hematocrit of intact red cells. The PT panels were made using blood from single donors with natural endogenous levels or by enriching single-donor whole blood specimens with one or more purified analytes at predetermined levels. The amino acid PT specimens were dispensed on S&S Grade 903 Lots W941, W961, and W001 filter papers (Figure 3). The acylcarnitine PT specimens were dispensed on S&S Grade 903 lot W961 filter paper. The DBS specimens were wrapped in glycine paper and packaged in zip-closed metallized plastic bags along with desiccant. The specimen bags along with instructions for analysis, and data-report forms were all enclosed with the shipment (Figure 4).

FIGURE 4. Packing cards.

REPRODUCIBILITY

Periodically, the NSQAP will provide a PT event that includes a duplicate specimen challenge in the same shipment or in consecutive shipments to check reproducibility within runs or between shipments. Extensive efforts and continuous checks are made to ensure the stability of the DBS materials during storage and shipment. We find that reproducibility checks add a reliability component to the list of certifying requirements for the quality of our DBS specimens. The bar charts (Figures 5a, 5b) demonstrate the mean reproducibility of specimens from two quarterly distributions of the same DBS pool lot. Good reproducibility is demonstrated between the two quarters for both amino acids and acylcarnitines specimens.

CUTOFF VALUES

Participants are asked to provide their cutoff value for each analyte tested. The cutoff value is defined as the decision level for sorting test results that are reported as presumptive positive (outside limits) from results reported as negative (within limits).

A presumptive-classification grading component was added to the MS/MS PT program for amino acids.

The distributions of reported amino acids cutoff values for participants are illustrated in Figures 6a-6f. Figures 7a-7g illustrate the distribution of all acylcarnitine cutoff values reported by participating laboratories. Some participants do not report a cutoff value to us. The mean cutoff values were calculated from cutoff data submitted on data report forms from Quarter 4, 2002.

The number of reported cutoff values varied from 14 laboratories reporting Valine (Val) cutoff values to 18 laboratories reporting Phenylalanine (Phe) cutoff values. The number of laboratories reporting acylarnitine cutoff values also varied from 14-20 reported cutoffs per acylcarnitine. Even though there are still some extreme outliers, the distributions of cutoff values for amino acids and acylcarnitines are moving closer in agreement among participants. The cutoff values may still continue to vary due to differences in derivatization methodologies and internal standard sources. Tables are provided for easy reference to the calculated cutoff means, medians, and minimum-maximum ranges for reported amino acids (Table 1) and acylcarnitine cutoff values (Table 2). The tables were created using cutoff data submitted in Quarter 4, 2002, from domestic participants only. These cutoff data can be used as a reference guide while laboratory specific cutoffs are being established as well as providing general information about presumptive classification decisions used by newborn screening laboratories.

The amino acid component of the MS/MS PT program expanded from submission of only quantitative data to including a qualitative assessment for each specimen in Quarter 4, 2002. The NSQAP will apply the laboratory-reported specific cutoff values, when available, to our grading algorithm for clinical assessments. When a laboratory's assessment differs from the CDC assessment the following steps are taken: (1) Determine the assessments for the CDC assayed value first by using the CDC cutoff and then by using the lab's cutoff value. (2) Compare the two assessments of the CDC assayed value. (3) If the two assessment values are the same, the lab assessment is incorrect, and either a false positive (FP) or false negative

Continued to Page 8

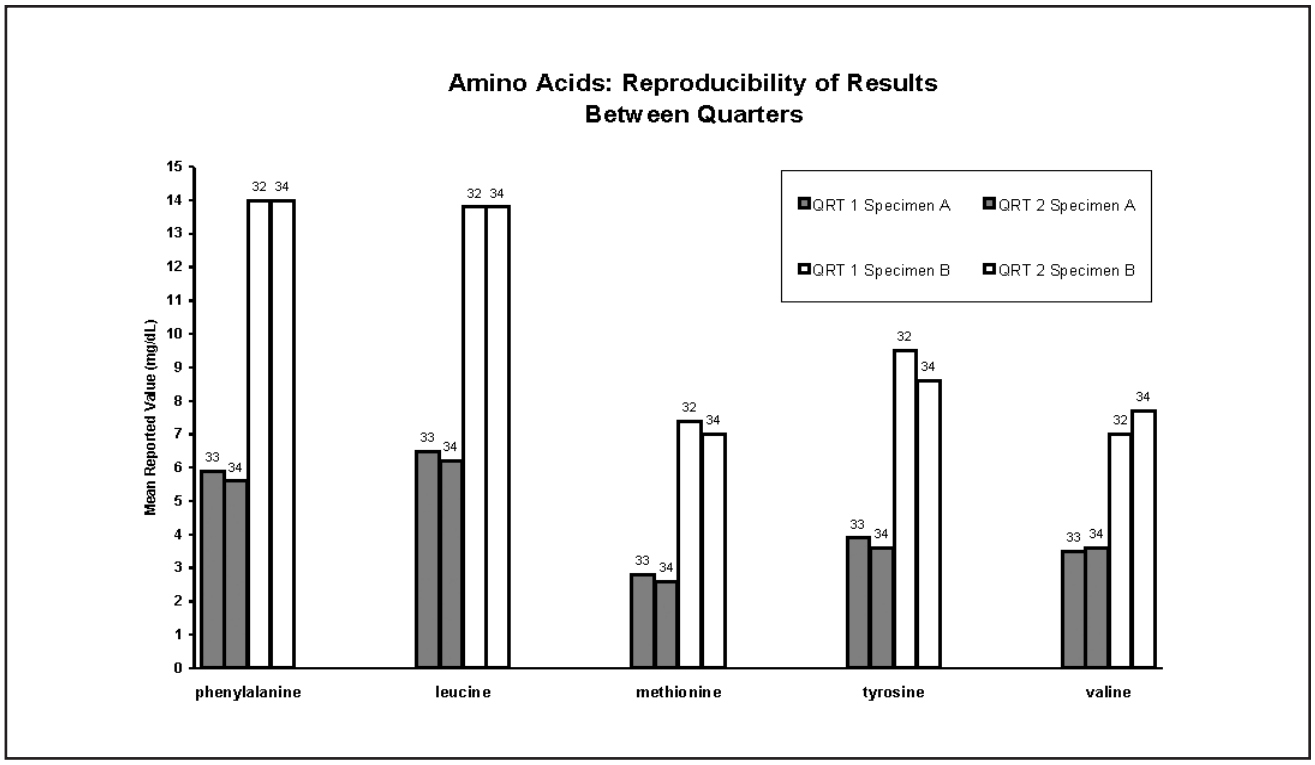

FIGURE 5a. Amino Acids: Mean Reproducibility of Pool A and Pool B Between Quarters Among All Participants.

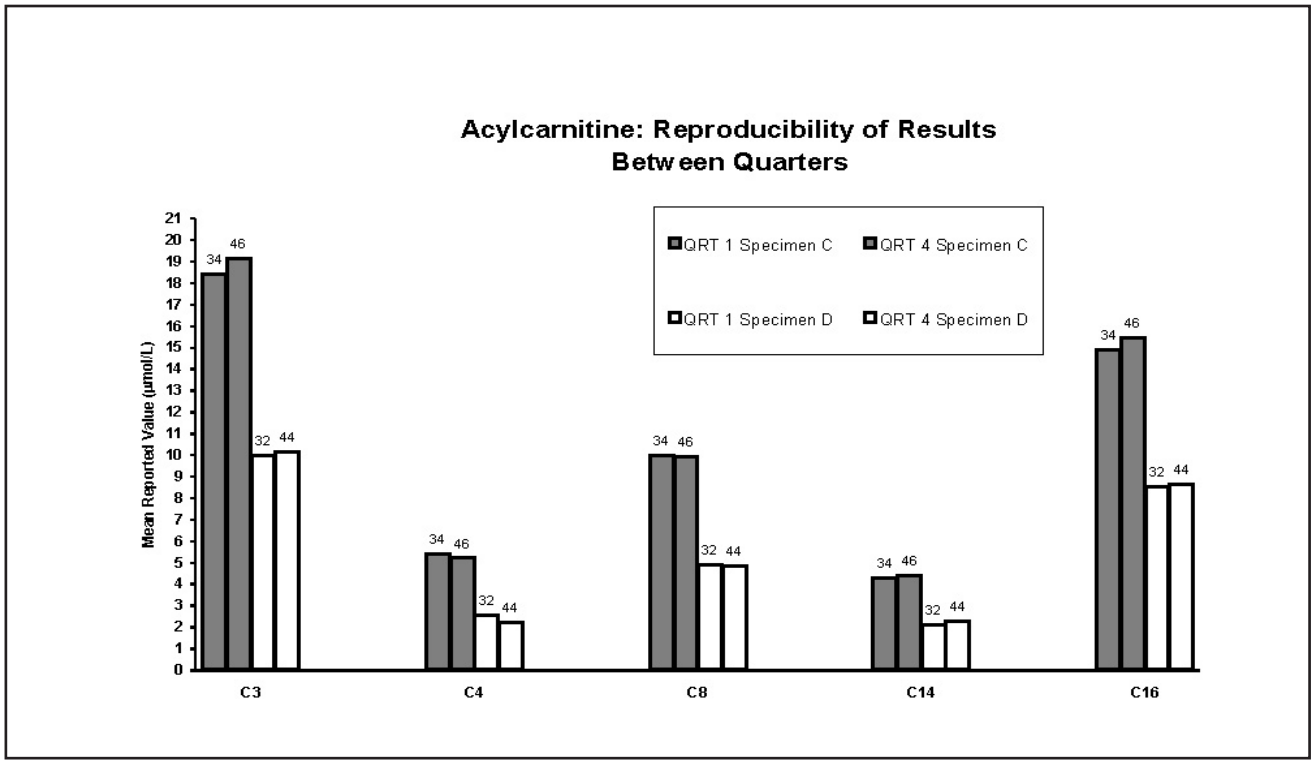

FIGURE 5b. Acylcarnitines: Mean Reproducibility of Pool C and Pool D Between Quarters Among All Participants.

The numbers of observations from which the mean reported concentrations were determined are shown above the bars.

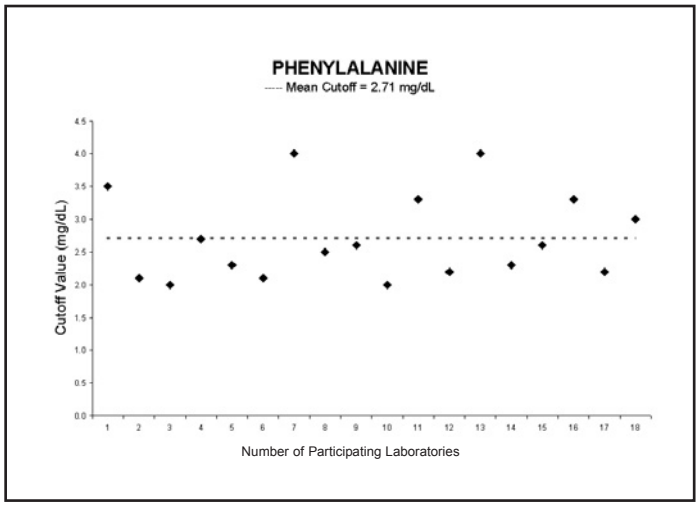

Figure 6a. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

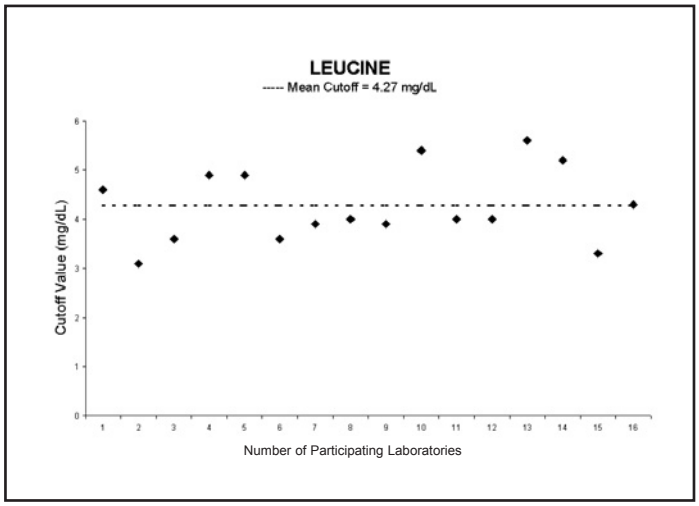

Figure 6b. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

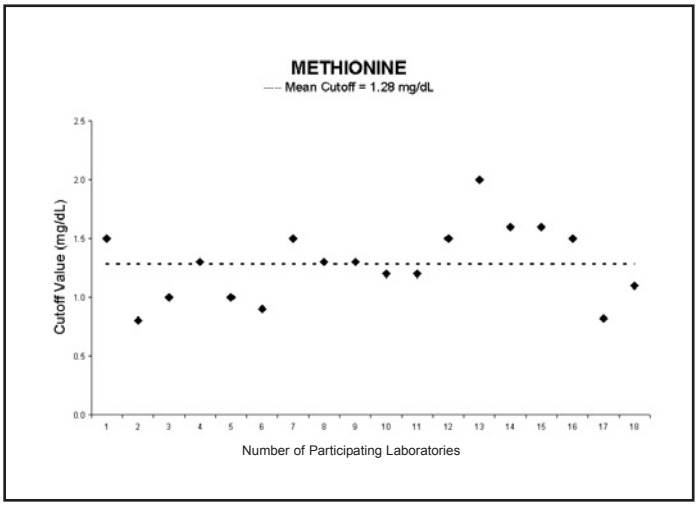

Figure 6c. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

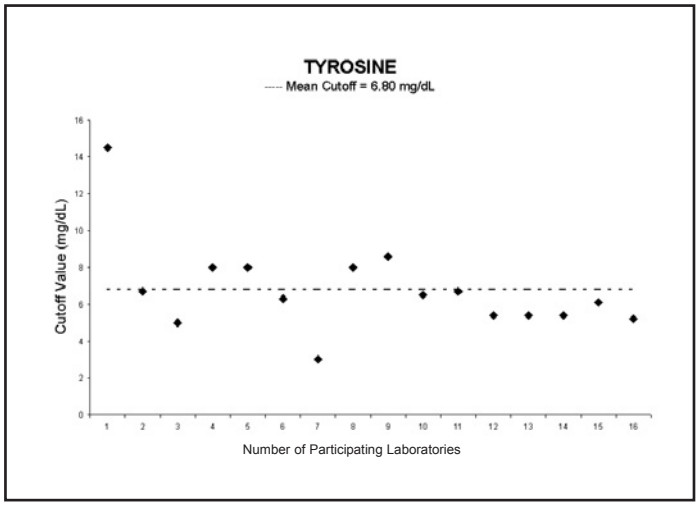

Figure 6d. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

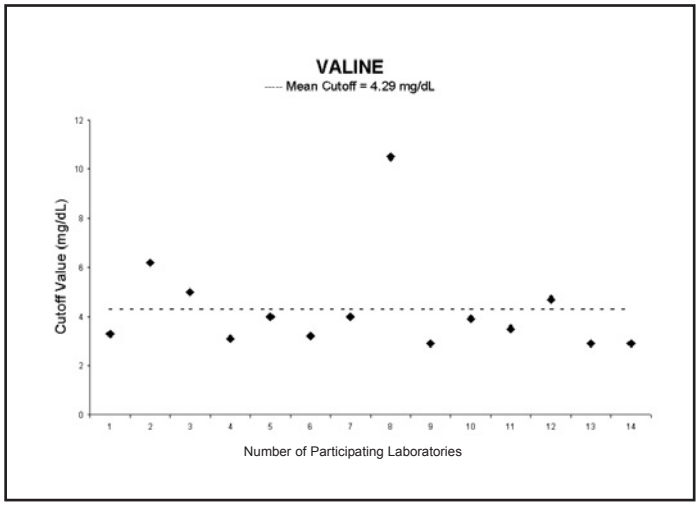

Figure 6e. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

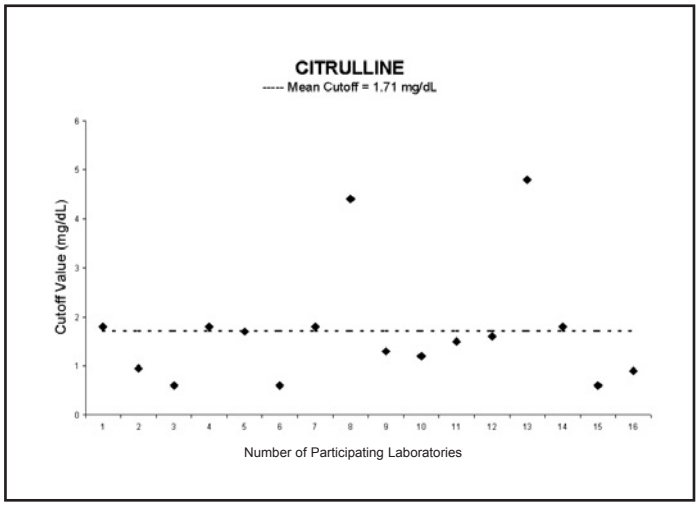

Figure 6f. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

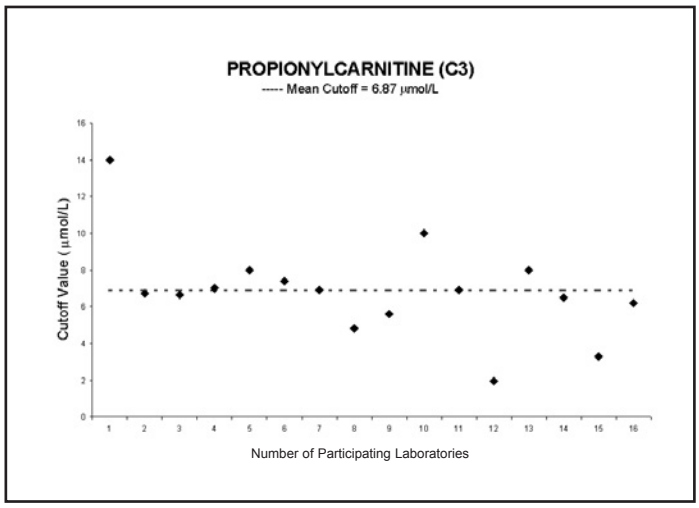

Figure 7a. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

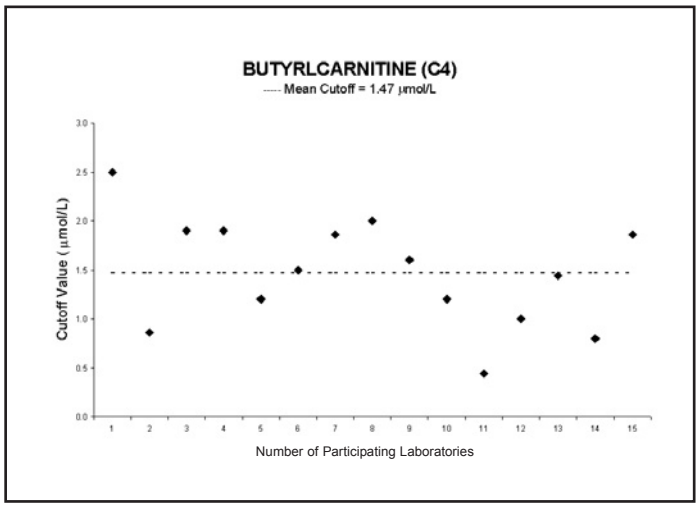

Figure 7b. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

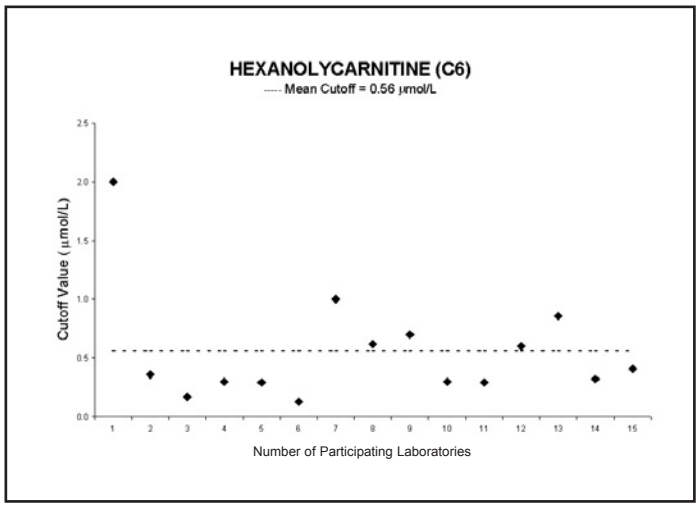

Figure 7c. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

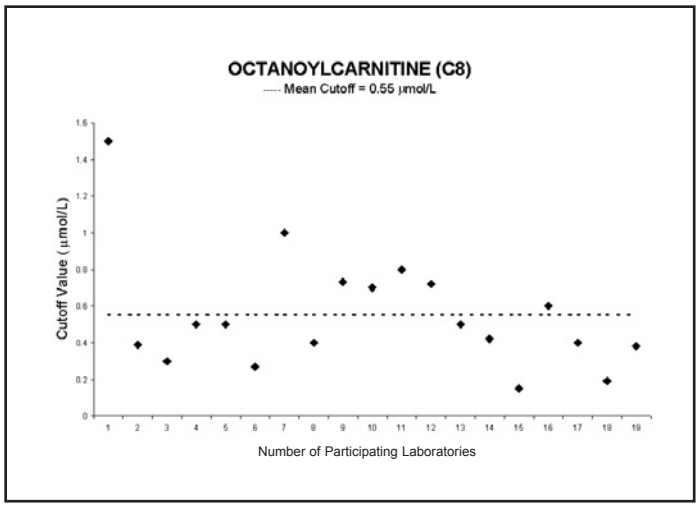

Figure 7d. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

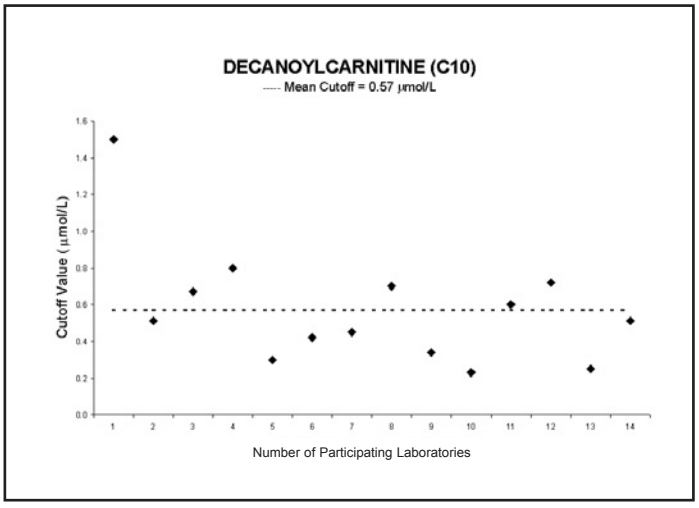

Figure 7e. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

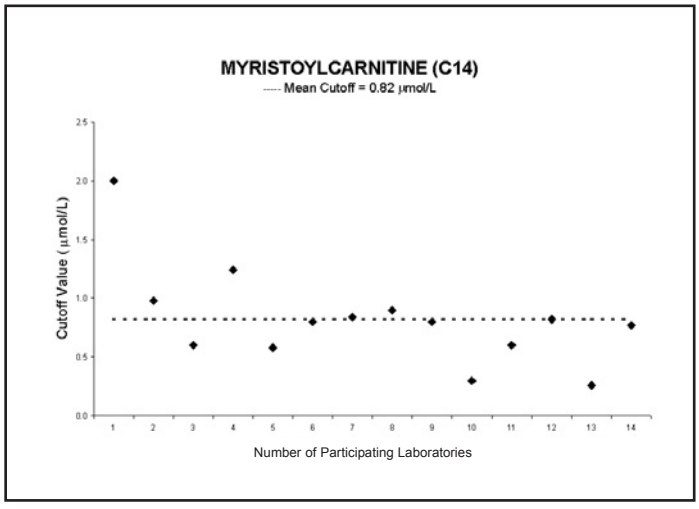

Figure 7f. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

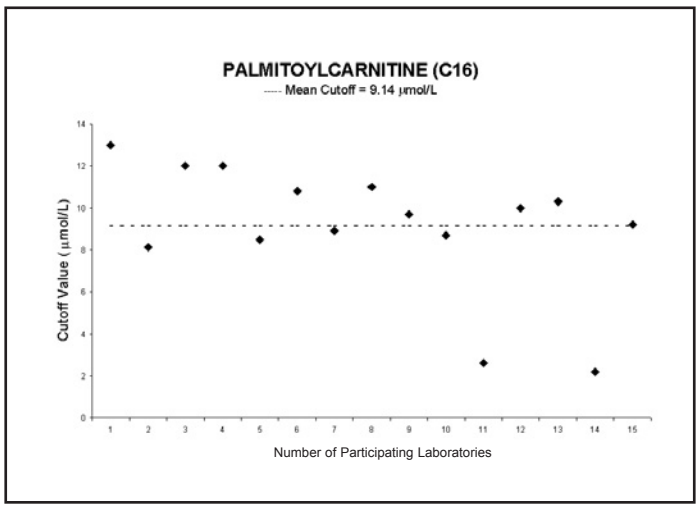

Figure 7g. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (µmol/L)

The calculated "median" cutoff value is included along with the "mean" cutoff value to show possible skewing of the mean value due to a very low or a very high cutoff value.

	MEAN µmol/L	MEDIAN µmol/L	MIN/MAX µmol/L		MEAN mg/dL	MEDIAN mg/dL	MIN/MAX mg/dL
Phenylalanine	164	158	121-242		2.7	2.6	2.0-4.0
Leucine	328	305	236-427		4.3	4	3.1-5.6
Methionine	87	87	54-134		1.3	1.3	0.8-2.0
Tyrosine	375	353	166-800		6.8	6.4	3.0-14.5
Valine	368	316	248-898		4.3	3.7	2.9-10.5
Citrulline	97	91	34-274		1.7	1.6	0.6-4.8

TABLE 1. Domestic Amino Acid Cutoff Value Statistics.

	MEAN µmol/L	MEDIAN µmol/L	MIN/MAX µmol/L
C3	6.87	6.82	1.93-14.00
C4	1.47	1.5	0.44-2.50
C5	---	---	---
C5DC	---	---	---
C6	0.56	0.36	0.13-2.00
C8	0.56	0.5	0.15-1.50
C10	0.57	0.51	0.23-1.50
C14	0.82	0.8	0.26-2.00
C16	9.14	9.7	2.20-13.00

TABLE 2. Domestic Acylcarnitine Cutoff Value Statistics.

(FN) is reported. (4) If the two assessment values are different, the lab's assessment is accepted due to cutoff consideration (CC). When a cutoff value is not supplied by the participant we will use the NSQAP-assigned working cutoff values that are based on the calculated domestic mean cutoff values.

The PT program for tandem mass spectrometry measurements will expand to include the clinical assessments for acylcarnitines by Quarter 3, 2003. The reporting of cutoff values is highly encouraged since the cutoff plays an important role in the evaluation process. The cutoff value is also used by NSQAP to guide the analytical enrichment levels for production of the PT specimens for future use.

PARTICIPANT RESULTS

Amino Acids

The following graphics (Figures 8-13) illustrate the assayed values submitted for each amino acid analyte by participant laboratories, domestic and foreign combined. Each analyte graphic shows a mean cutoff value represented by a solid line and a median cutoff value represented by a dotted line. The decision to reference the "median" cutoff value along with the "mean" cutoff value was to show possible skewing of the mean due to one very high or very low cutoff value. (See section on determining appropriate cutoffs). Assayed values from the PT event for Quarter 4, 2002, were plotted against the overall mean and median cutoff values. The values for the non-enriched specimens "0 mg/dL" show the measured endogenous concentrations for the analyte. When specimens are enriched with predetermined levels of pure analyte, the overall concentration can be higher due to the contribution of endogenous levels. Even though the inherent characteristics of DBS cause some variation among data values, differences in pre-analytic derivatization methods and internal standard materials also influence the measured concentrations. Inquiries in the form of questionnaires are periodically added to the NSQAP data-report forms as a means of collecting procedural information that will enable the sorting of data by these differences.

Quarter 4, 2002, participant results for amino acids show Phe results are in good agreement with regard to classifications. The non-enriched specimens reported Phe values below the mean cutoff value with one laboratory reporting a value above the mean cutoff value. The enriched specimens 4255 and 4253 containing 7 and 11 mg Phe/dL, respectively, show all results well above the mean cutoff value. Specimen 4252, enriched with 3 mg Phe/dL, shows all but one laboratory reporting above the cutoff value.

All but two Leucine (Leu) values for the non-enriched Leu specimens are clearly below the mean cutoff value, and results from the Leu specimens enriched with 7 mg and 11 mg Leu/dL of blood, respectively, fall above the mean cutoff value and are clearly outside limits. Results from the Leu specimens enriched with >3 mg Leu/dL of blood suggest that quantitative results would be scattered above and below the mean cutoff value as expected. The pattern of Methionine (Met) results was similar to that of Leu. The values for the non-enriched specimens all fall below the mean cutoff value; the reported values for the specimens 2.5, 3.0, and 6 mg Met/dL of blood are classified clearly above the mean cutoff value; and the reported values for the specimen enriched with >1 mg Met/dL but <2.5 mg Met/dL of blood would be scattered above and below the mean cutoff value for Met as expected.

Tyrosine (Tyr) results for specimens enriched with 0 to 4 mg Tyr/dL of blood fall below the mean cutoff for Tyr, whereas results for the Tyr specimen enriched with 8 mg Tyr/dL of blood are scattered around the mean cutoff value of 6.8 mg Tyr/dL; thus, no clearly abnormal Tyr challenge was presented in this survey.

All but one reported value fall below the mean cutoff for the non-enriched Val specimens. The specimen enriched with 2 mg Val/dL of blood shows all but two laboratories were below the mean cutoff value. The specimen enriched with 3 mg Val/dL of blood shows results evenly distributed above and below the mean cutoff value of 4.29 mg Val/dL of blood; and for the specimen enriched with 6 mg Val/dL of blood, all but five reported values are above the mean cutoff suggesting that results from specimens enriched between > 3 to < 6 mg Val/dL of blood would be scattered above and below the mean cutoff value.

Citruilline (Cit) results for all non-enriched specimens are below the mean cutoff. With the exception of one result, all reported results for the specimen enriched with 0.5 mg Cit/dL of blood fall below the mean cutoff value. The specimen enriched with 1 mg Cit/dL of blood shows two participants reporting values above the mean cutoff and all other laboratories reporting values below the mean cutoff. The specimen enriched with 2.5 mg Cit/dL of blood shows that many participants fall around the mean cutoff value of 1.71 mg Cit/dL, therefore suggesting that a higher enrichment should be used to achieve a clear-cut abnormal PT specimen for Cit.

Continued to Page 15

Figures 8a-8e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Phenylalanine

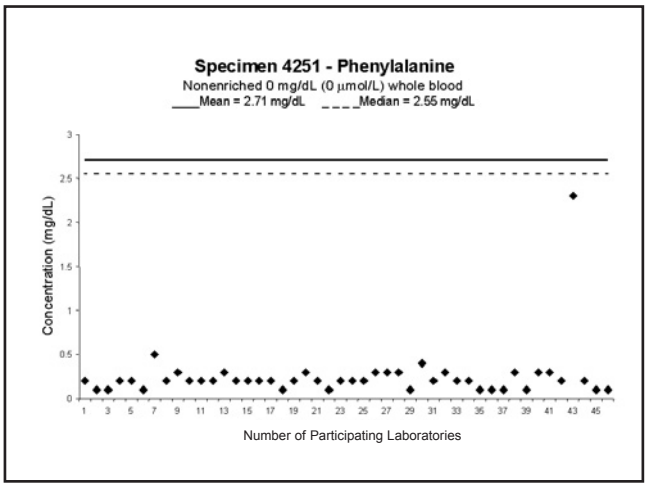

Figure 8a.

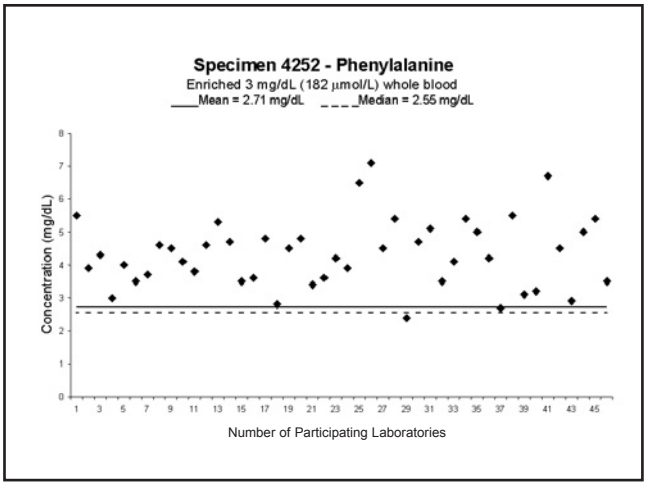

Figure 8b.

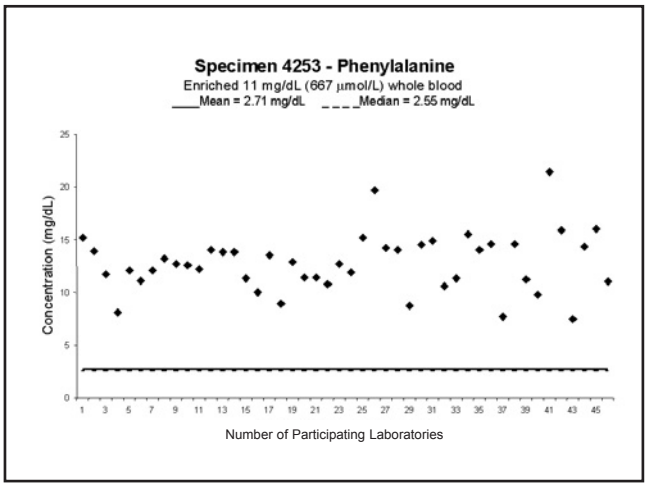

Figure 8c.

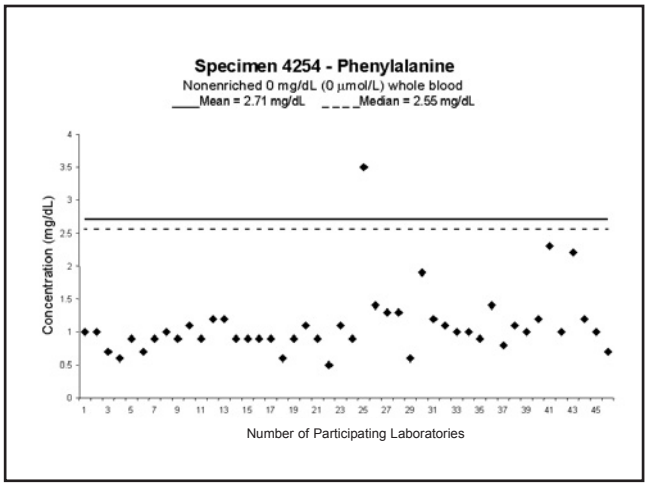

Figure 8d.

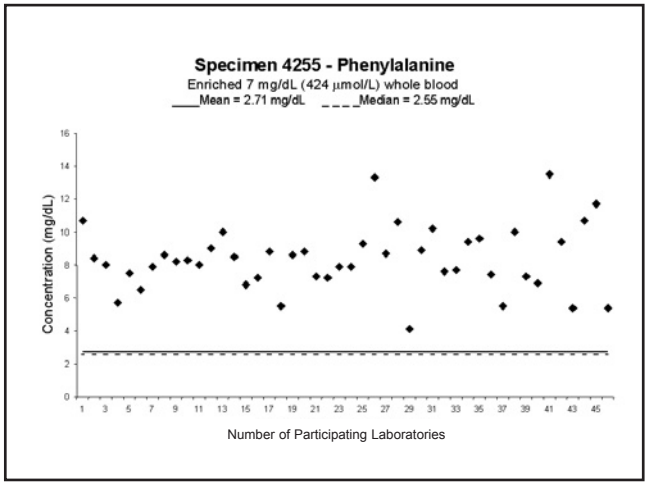

Figure 8e.

Figures 9a-9e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Leucine

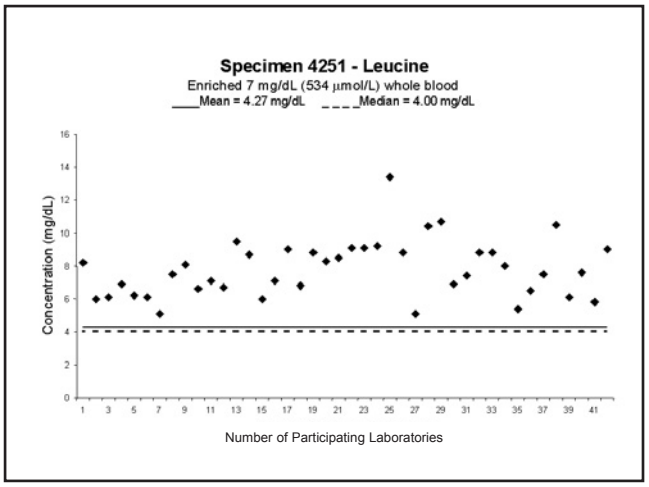

Figure 9a.

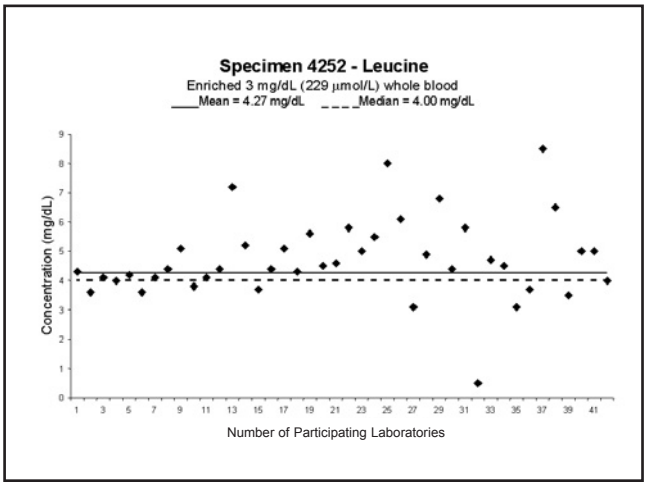

Figure 9b.

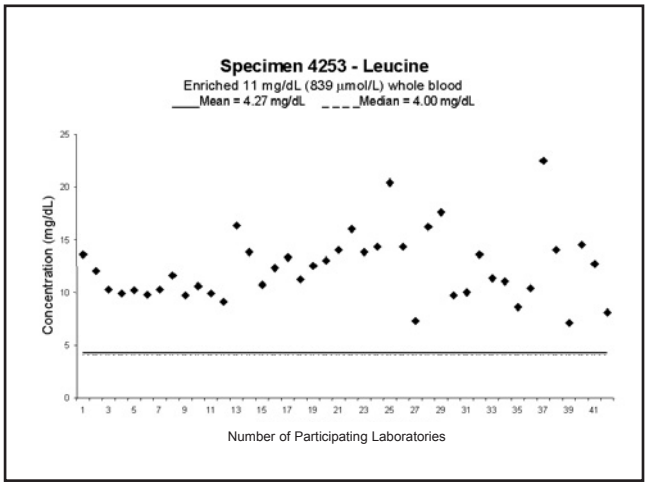

Figure 9c.

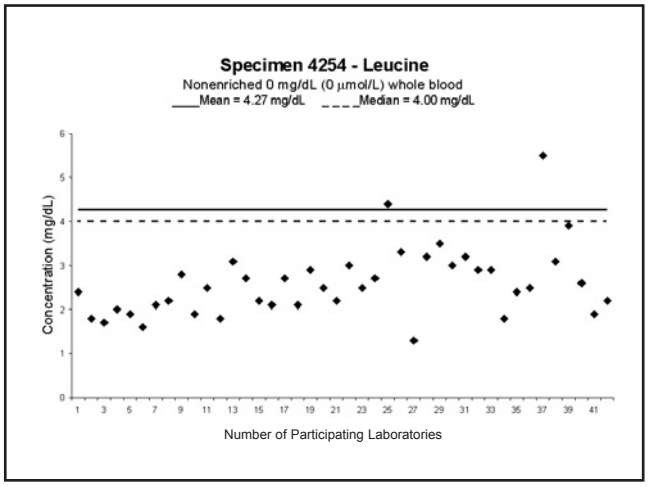

Figure 9d.

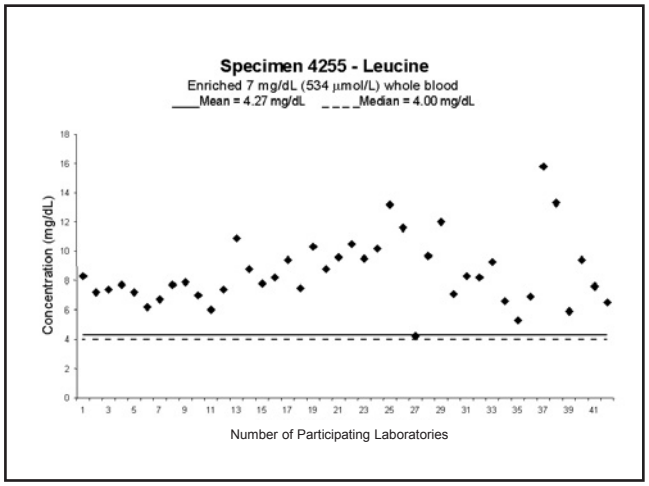

Figure 9e.

Figures 10a-10e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Methionine

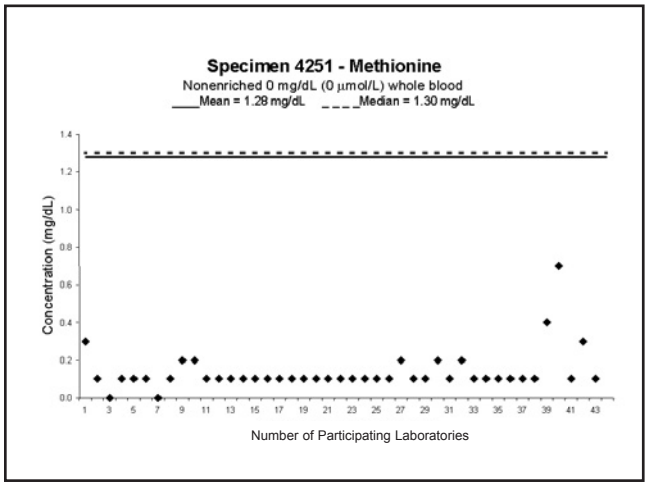

Figure 10a.

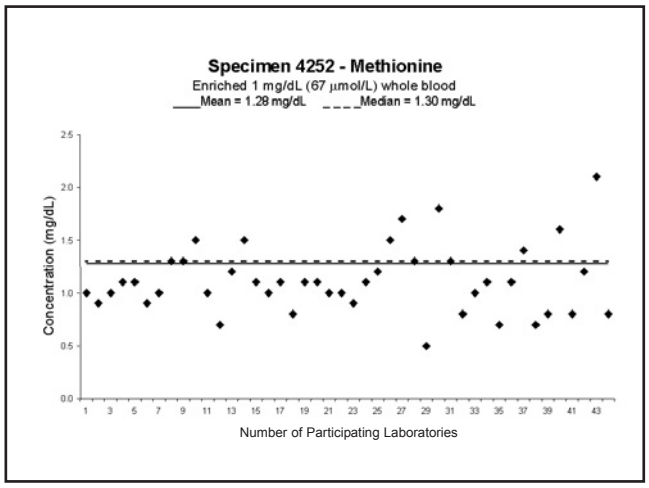

Figure 10b.

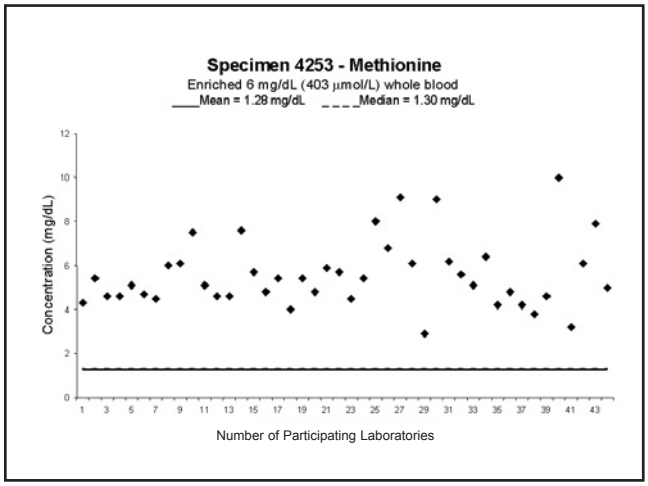

Figure 10c.

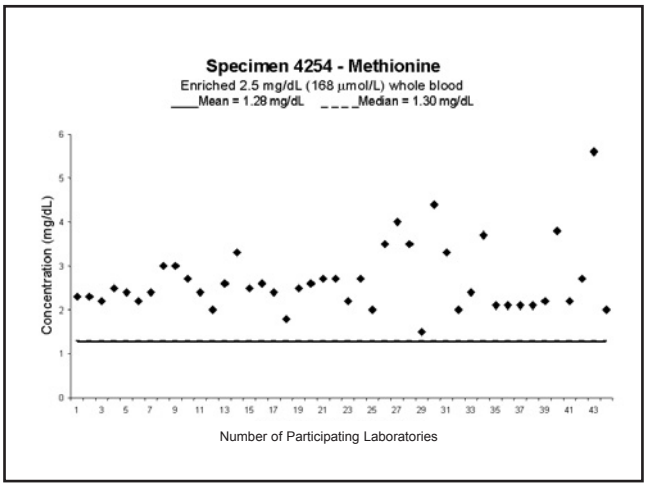

Figure 10d.

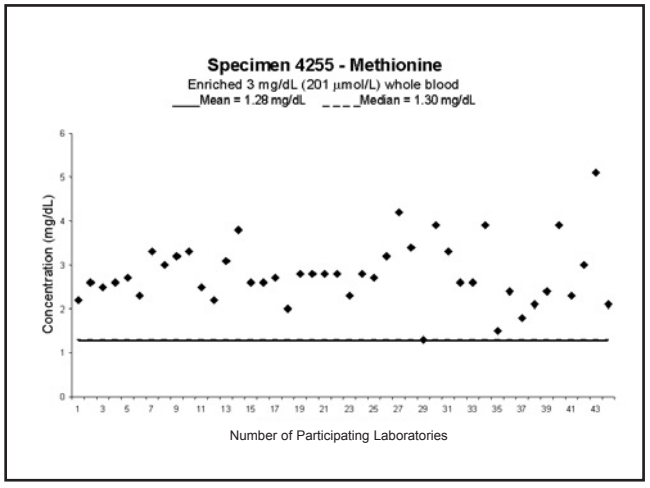

Figure 10e.

Figures 11a-11e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Tyrosine

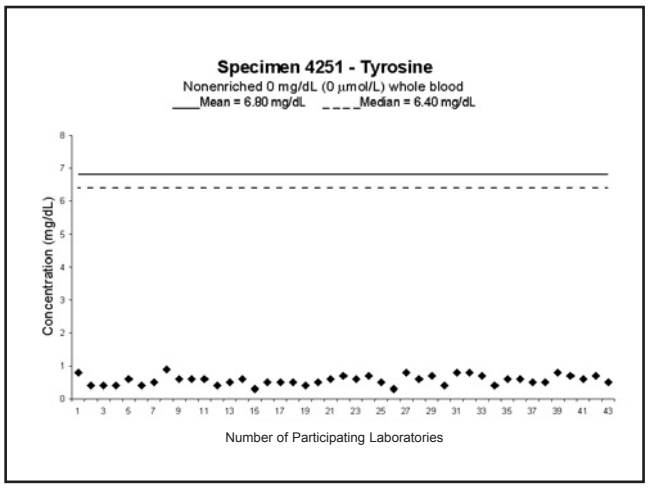

Figure 11a.

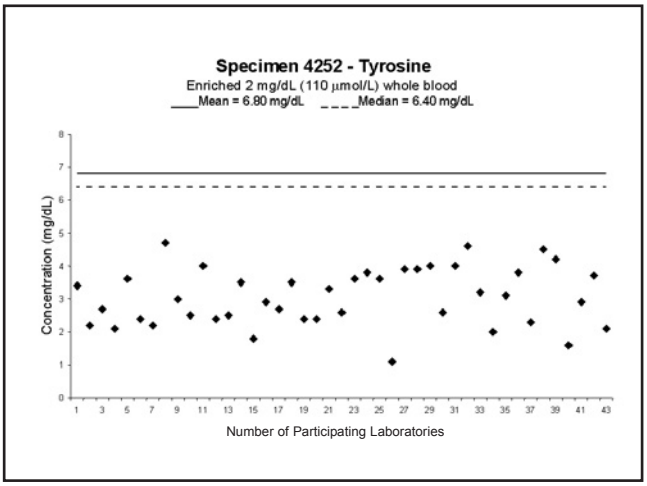

Figure 11b.

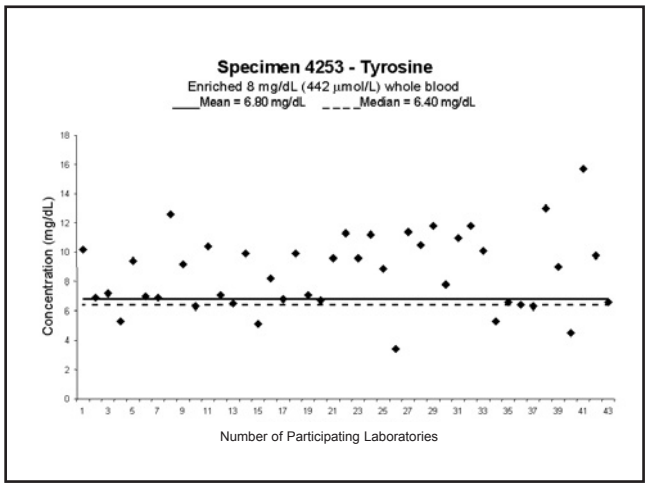

Figure 11c.

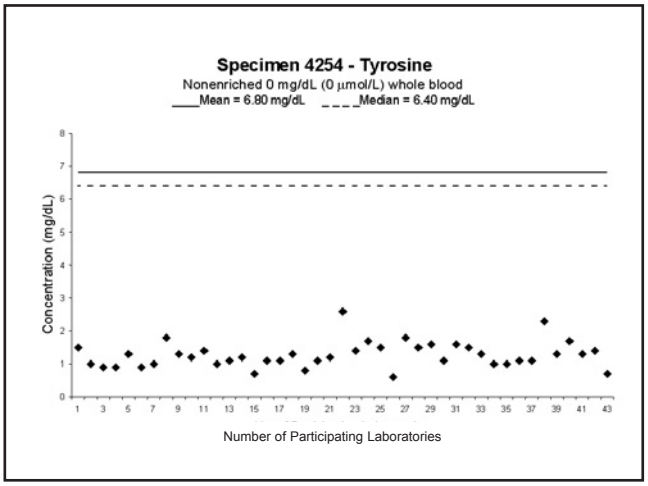

Figure 11d.

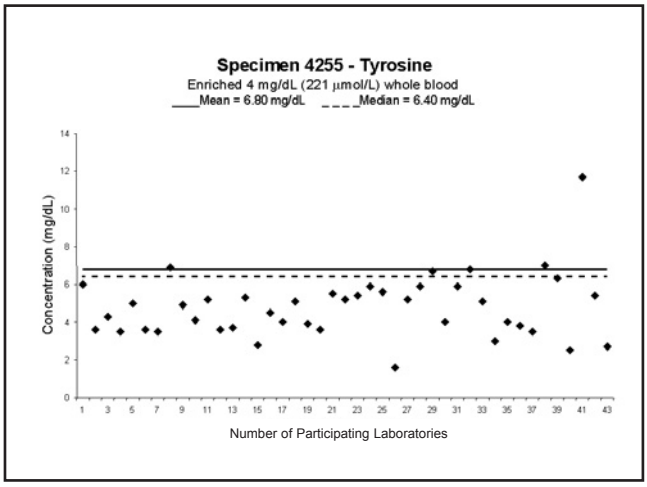

Figure 11e.

Figures 12a-12e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Valine

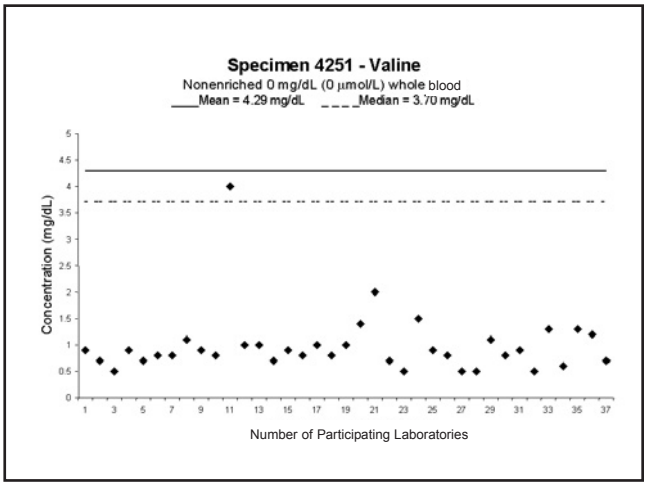

Figure 12a.

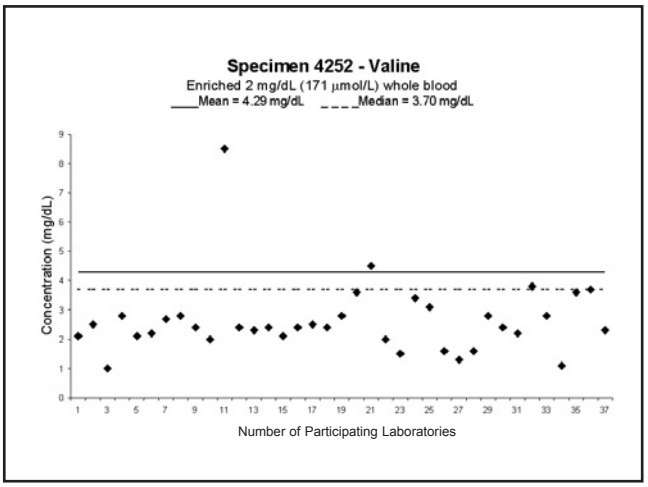

Figure 12b.

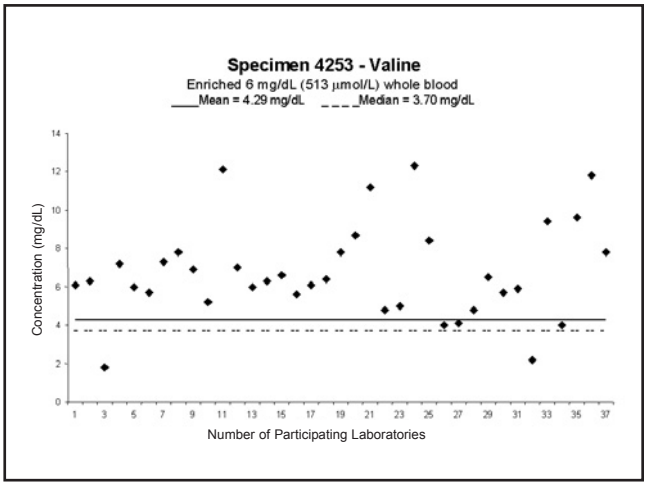

Figure 12c.

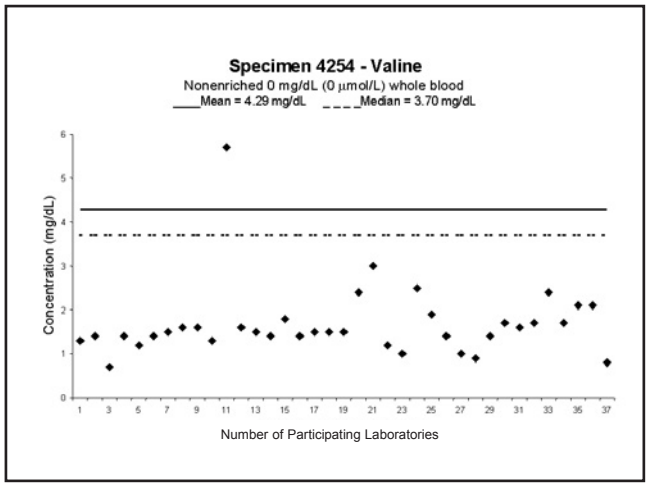

Figure 12d.

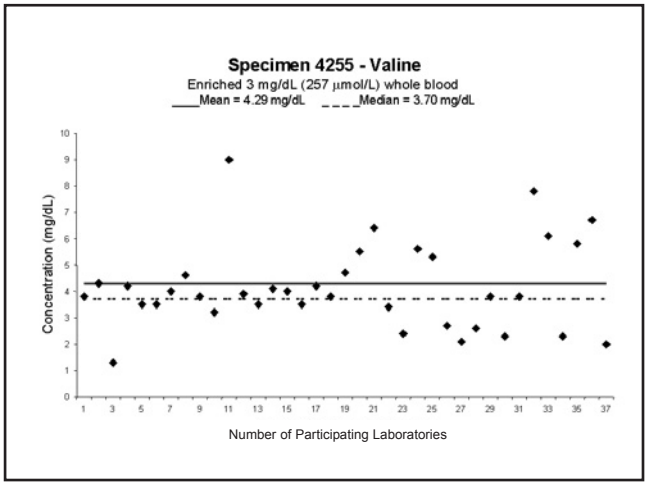

Figure 12e.

Figures 13a-13e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Citrulline

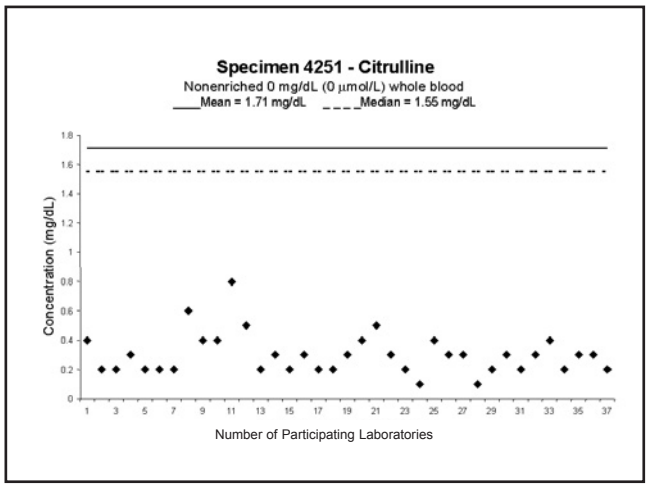

Figure 13a.

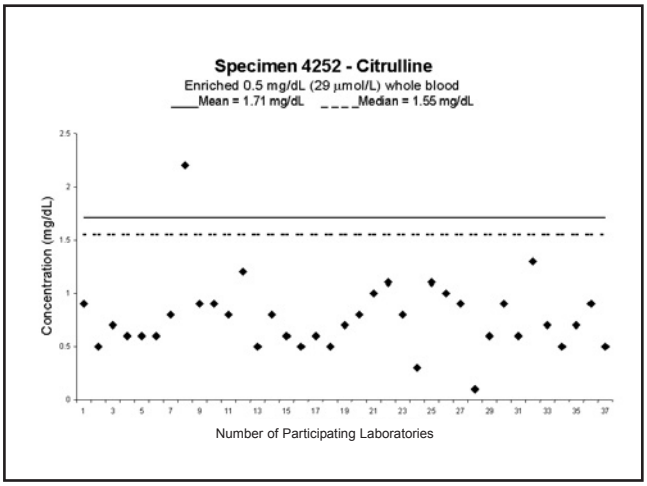

Figure 13b.

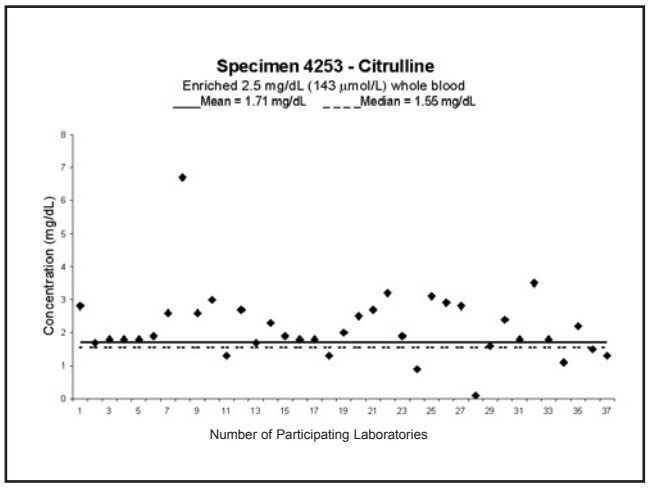

Figure 13c.

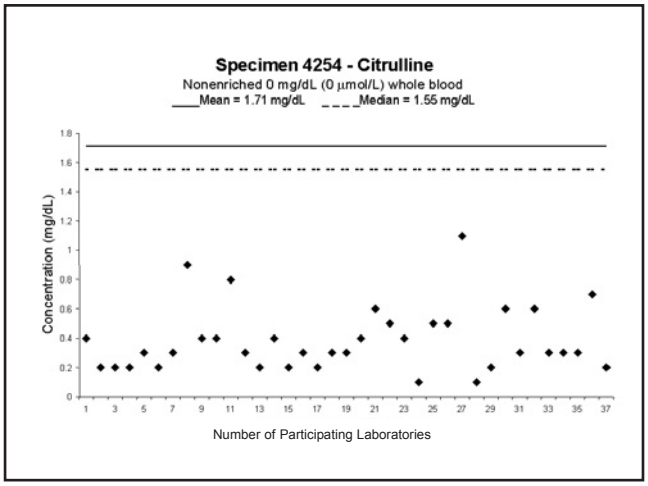

Figure 13d.

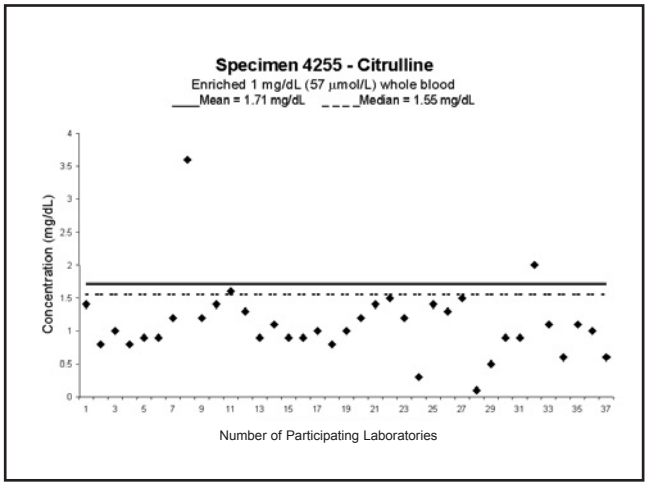

Figure 13e.

In cases where the distribution of participant results are above and below the mean cutoff value and if the consensus of reports is not greater than 80%, the specimen would be classified as a non-evaluated specimen.

Acylcarnitines

The acylcarnitine participant results are shown in reference to our calculated cutoff means and medians for report cutoffs (Figures 14-20). The graphs were produced using only Quarter 4, 2002, results.

The C3 (propionylcarnitine) results show that quantitative values reported for the non-enriched C3 specimens 4261, 4263, and 4265 are all well below the cutoff mean of 6.87 µmol C3/L. All reported values for the C3 specimen enriched with 12 µmol C3/L of blood with the exception of one laboratory's value are above the mean cutoff; and the ranges of quantitative values for the specimen enriched with 6 µmol C3/L show all but three laboratories reporting values above the mean cutoff.

The non-enriched C4 (butyrlcarnitine) results for specimens, 4261 and 4263, show all laboratories falling below the mean cutoff of 1.47 µmol C4/L; but the results for the non-enriched specimen 4265 show three laboratories reporting results above the mean cutoff. Results for specimen 4262 enriched with 2 µmol C4/L of blood show two laboratories reporting below the cutoff mean of 1.40 µmol C4/L and all the other laboratories reporting results above the mean cutoff. The C4 specimen enriched with 4 µmol C4/L shows all results above the mean cutoff as expected.

All results for the non-enriched C6 (hexanoylcarnitine) specimens 4261, 4262, and 4264 are well below the cutoff mean value of 0.56 µmol C6/L. The enriched C6 specimen 4265 shows all results reported above the mean cutoff value. The C6 specimen enriched with 0.3 µmol C6/L of blood shows all but two laboratories reporting in the expected range.

The results for the non-enriched C8 (octanoylcarnitine) specimen 4261 show all results well below the mean cutoff. The results for specimens enriched with 4, 8, and 12 µmol C8/L of blood show all values well above the mean cutoff. The results for the specimen enriched with 0.5 µmol C8/L of blood show a scattered distribution above and below the mean cutoff of 0.55 µmol C8/L of blood.

The results for non-enriched C10 (decanoylcarnitine) specimen 4261 show that all laboratory results are within expected limits; however, results for the non-enriched specimen 4264 shows seven (both domestic and foreign) laboratories reporting values above and below the mean cutoff of 0.57 µmol C10/L of blood. The specimen enriched with 0.5 µmol/L of blood clearly demonstrates an even distribution around the mean cutoff value of 0.57 µmol C10/L of blood. The C10 specimen enriched with 1 µmol C10/L of blood shows all results except one well above the mean cutoff value.

There are three non-enriched specimens for C14 (Myristoylcarnitine), 4261, 4263, and 4265. In each case there is a participant's result that is above the mean cutoff value of 0.82 µmol C14/L. The data for specimens enriched with 2 and 4 µmol C14/L of blood show all reported values fall well above the mean cutoff value. All reported values for the non-enriched C16 (palmitoylcarnitine) specimens fall below the mean cutoff value of 9.14 µmol C16/L of blood. Results for specimen 4264 enriched with 12 µmol C16/L of blood show all results falling above the mean cutoff. Results for specimen 4262 enriched with 6 µmol C16/L of blood show an even distribution below and above the mean cutoff value of 9.14 µmol C16/L of blood.

A summary of the performance evaluation errors is shown

When reporting cutoff values, we requested the decision level for sorting test results that are reported as presumptive positive (outside limits) from results reported as negative (within limits).

Figures 14a-14e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Propionylcarnitine (C3)

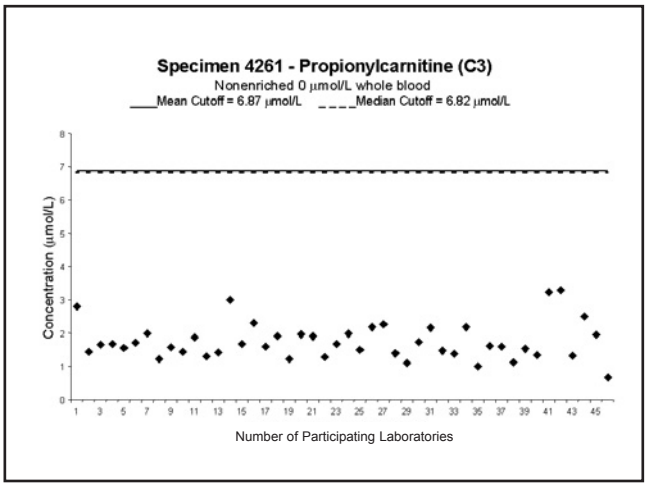

Figure 14a.

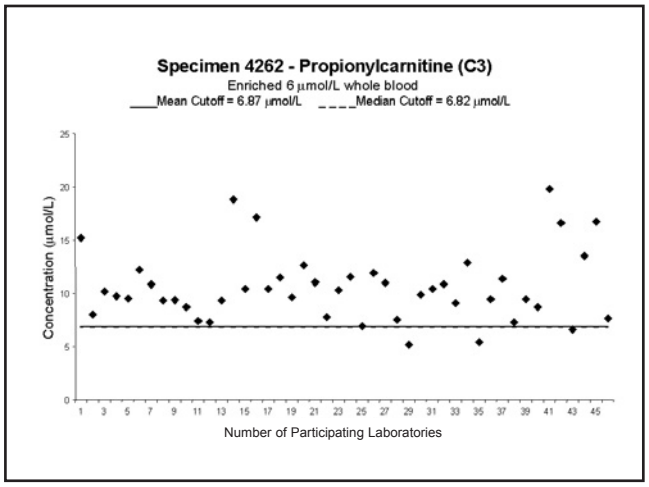

Figure 14b.

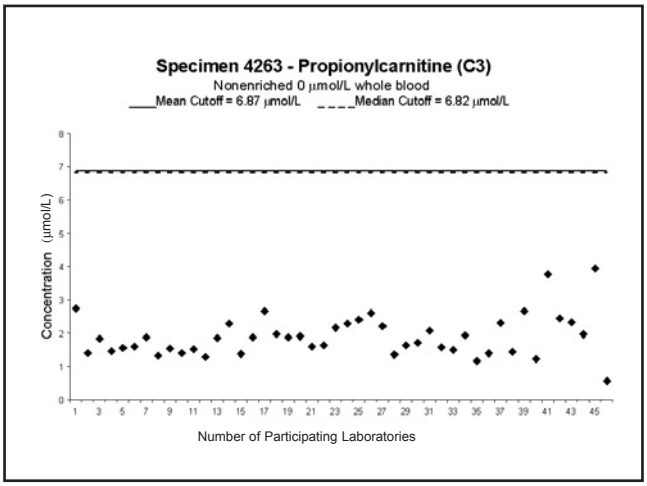

Figure 14c.

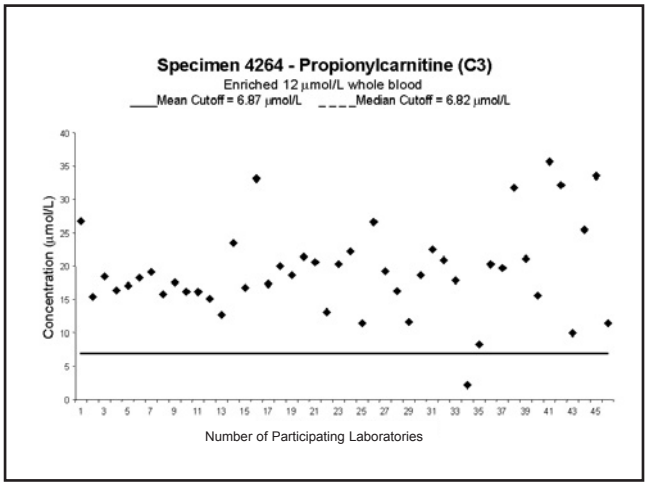

Figure 14d.

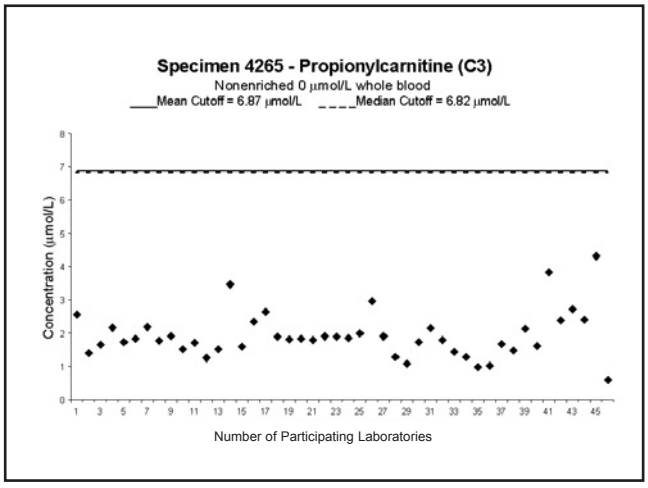

Figure 14e.

Figures 15a-15e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Butyrlcarnitine (C4)

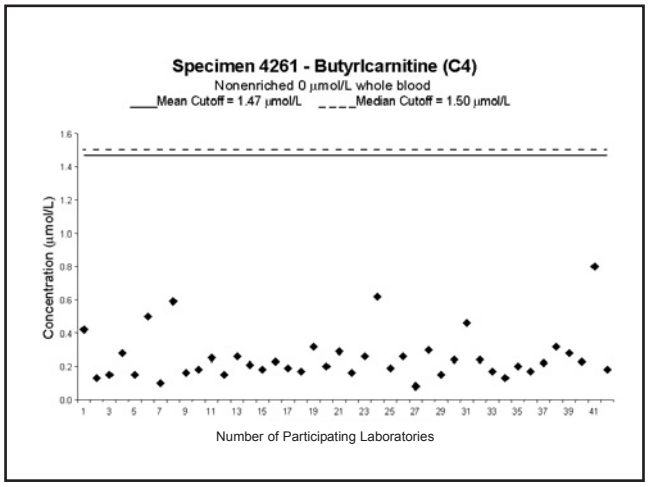

Figure 15a.

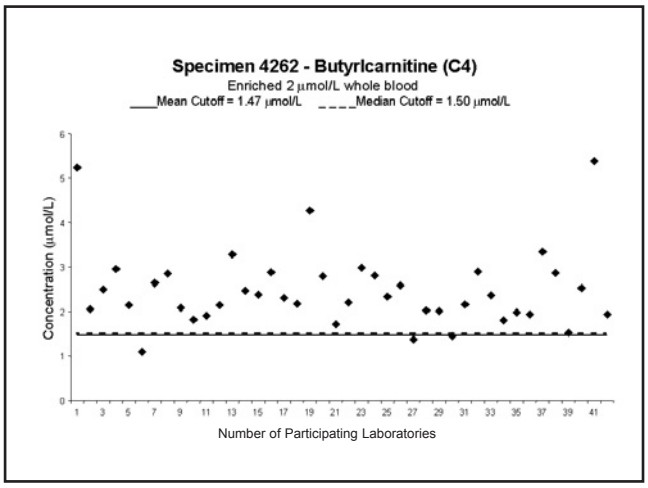

Figure 15b.

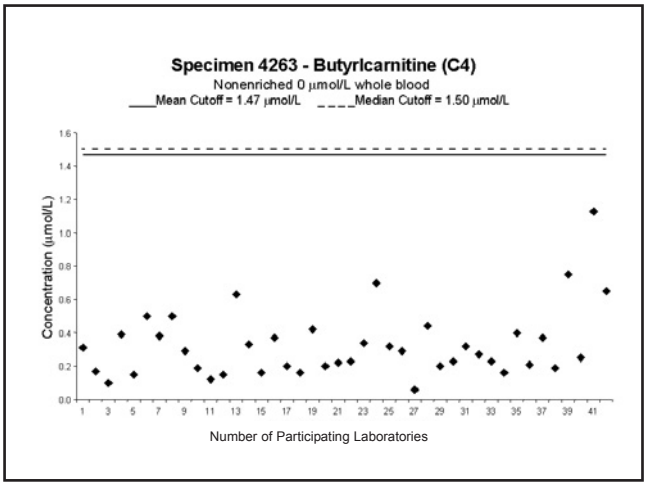

Figure 15c.

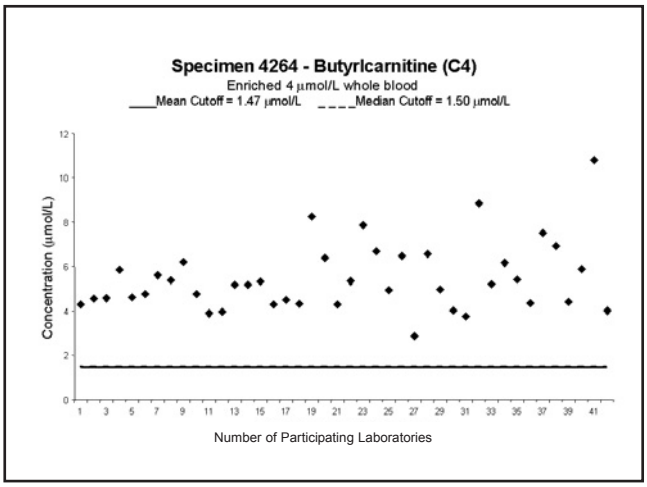

Figure 15d.

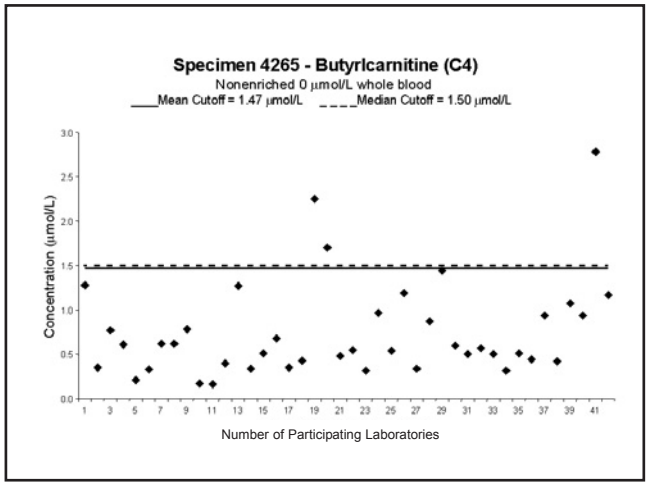

Figure 15e.

Figures 16a-16e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Hexanoylcarnitine (C6)

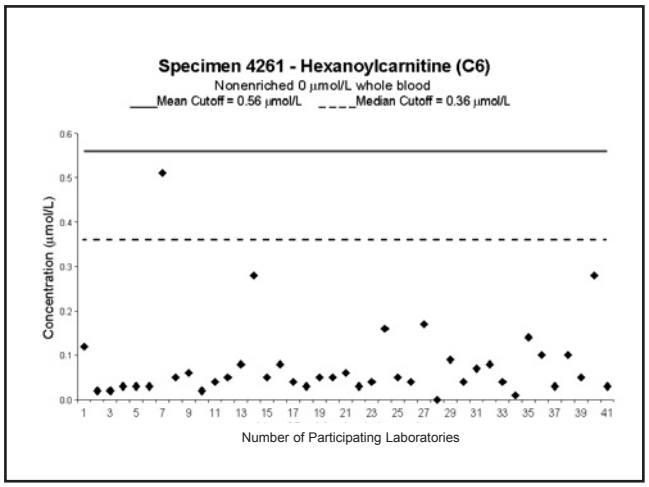

Figure 16a.

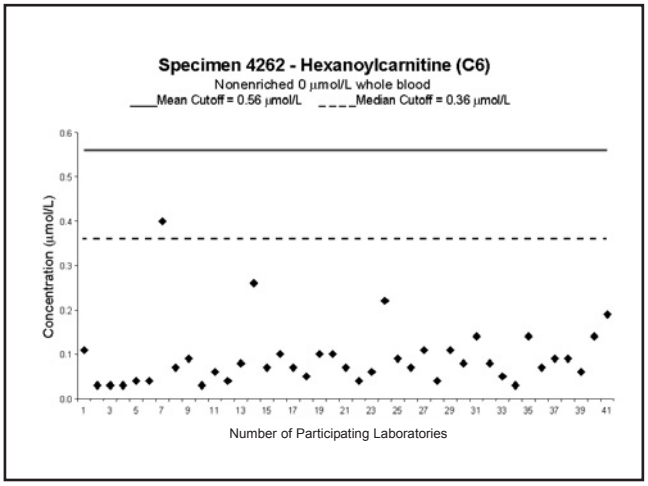

Figure 16b.

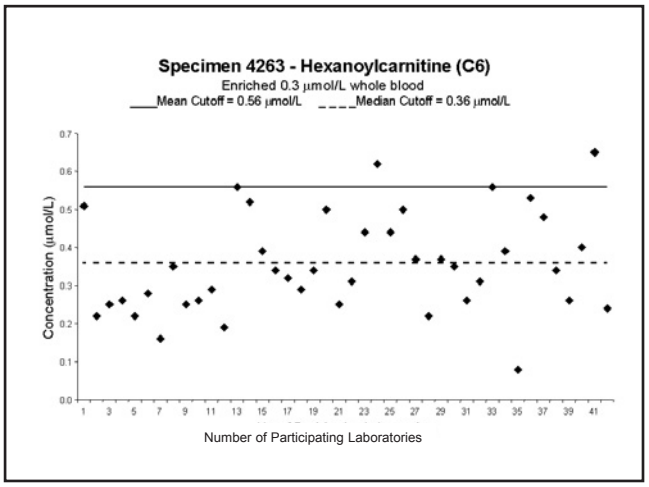

Figure 16c.

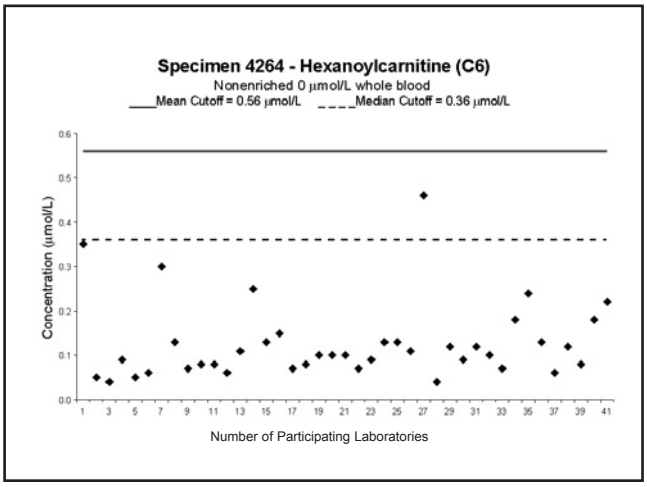

Figure 16d.

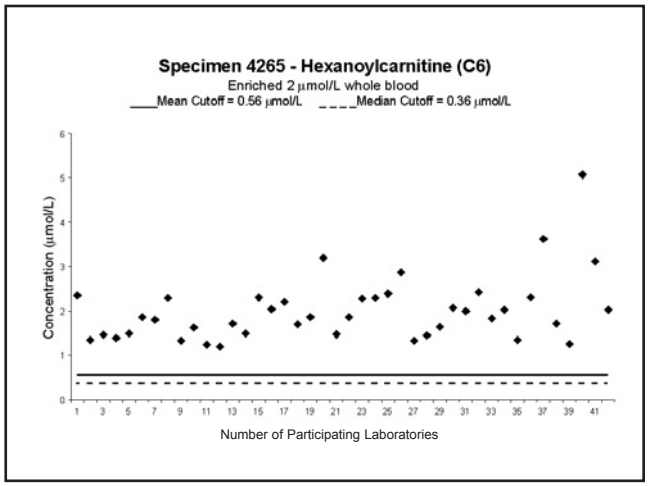

Figure 16e.

Figures 17a-17e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Octanoylcarnitine (C8)

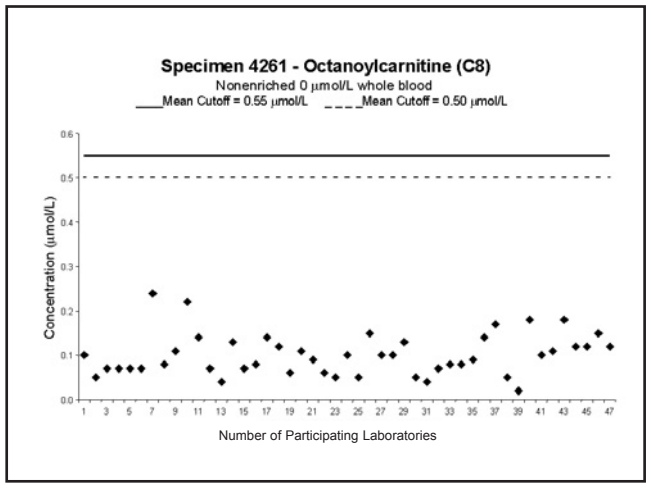

Figure 17a.

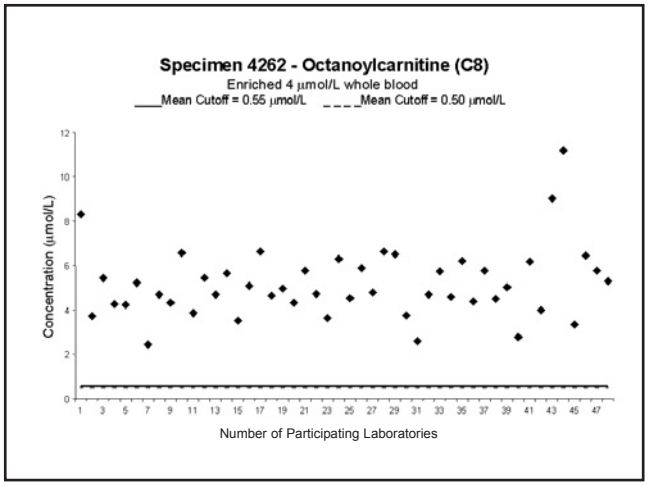

Figure 17b.

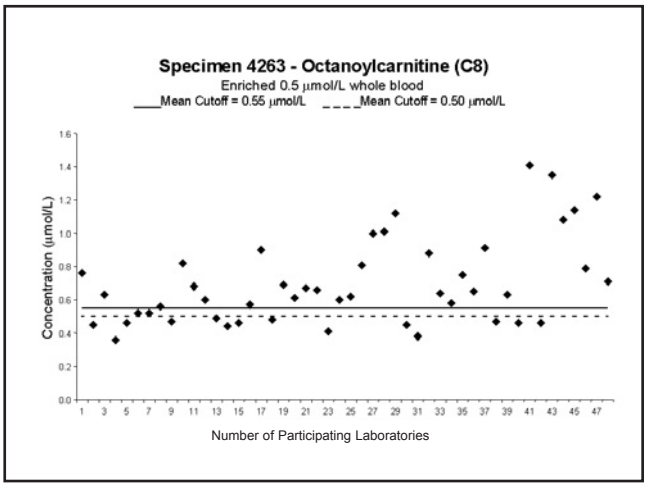

Figure 17c.

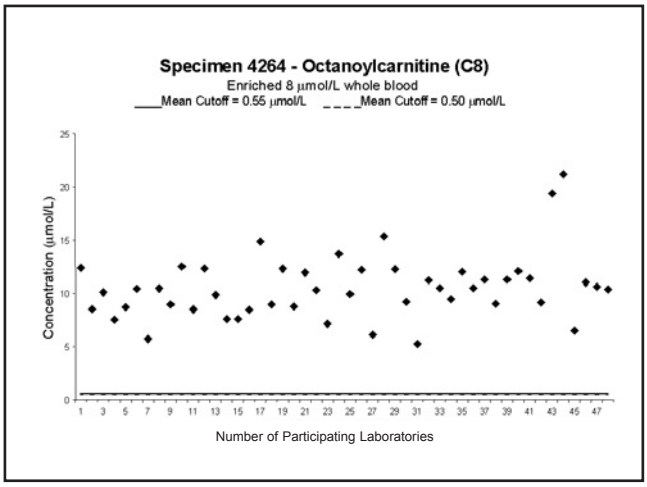

Figure 17d.

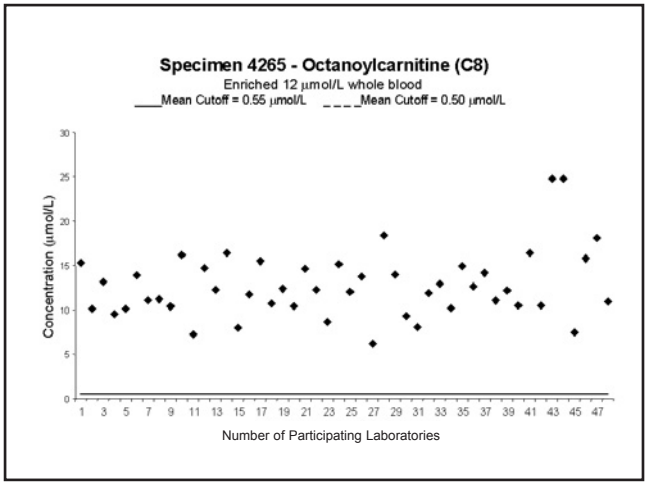

Figure 17e.

Figures 18a-18e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Decanoylcarnitine (C10)

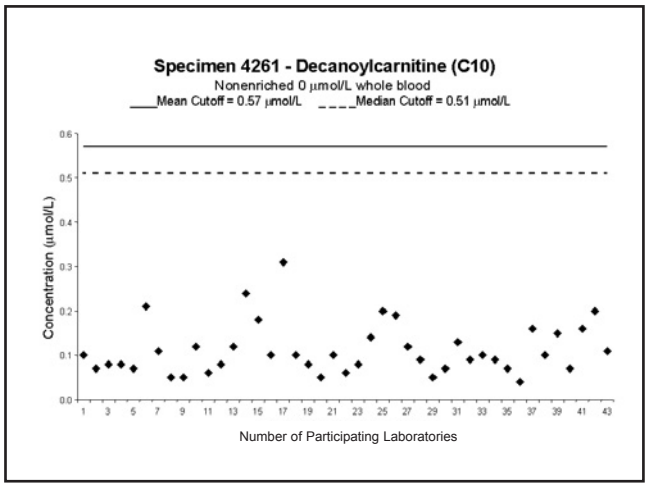

Figure 18a.

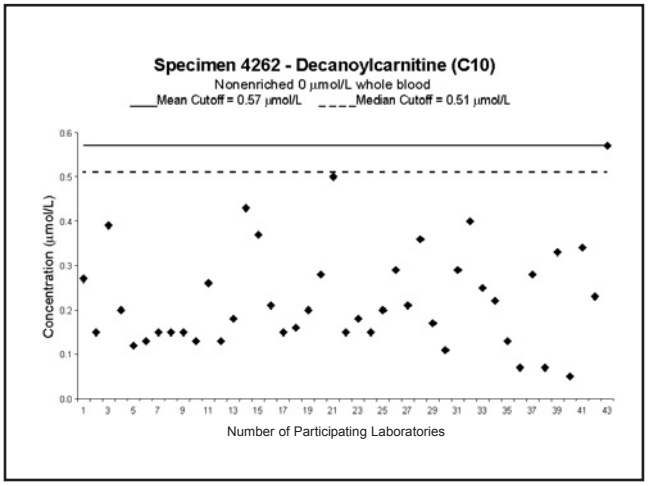

Figure 18b.

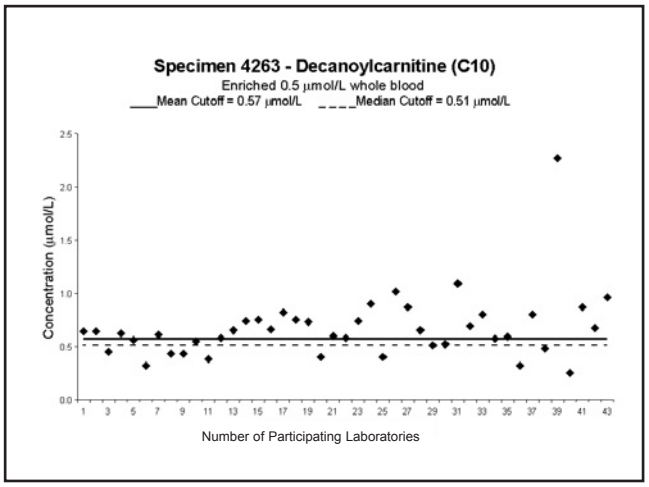

Figure 18c.

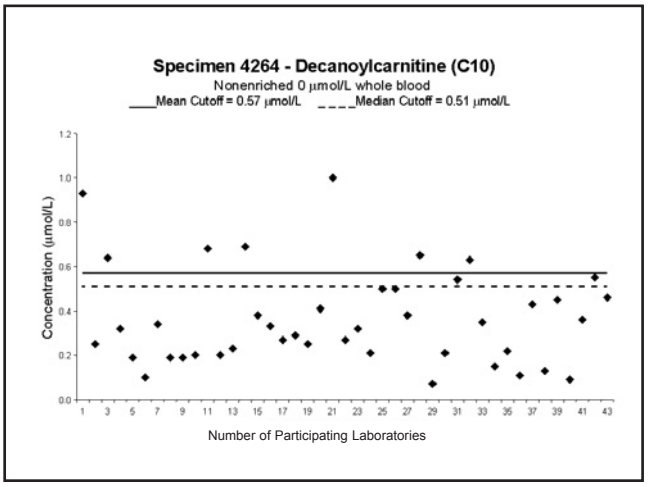

Figure 18d.

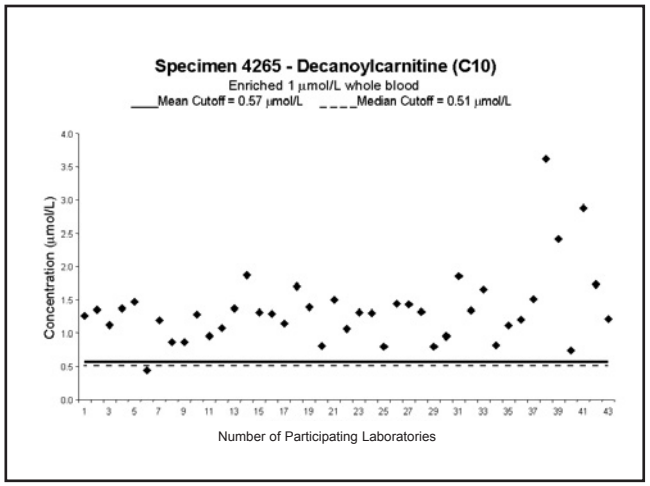

Figure 18e.

Figures 19a-19e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Myristoylcarnitine (C14)

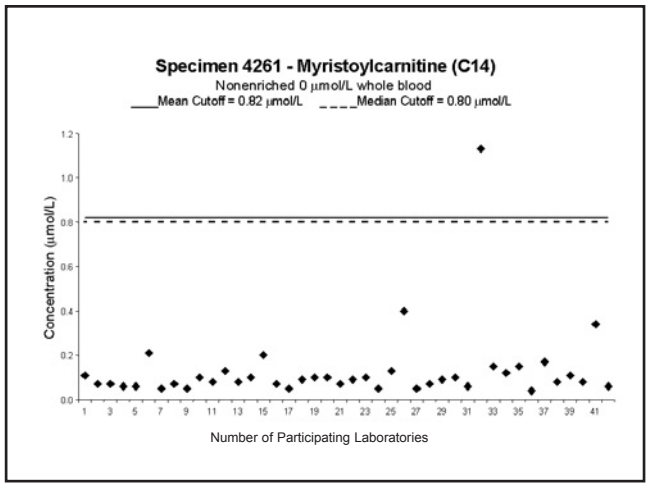

Figure 19a.

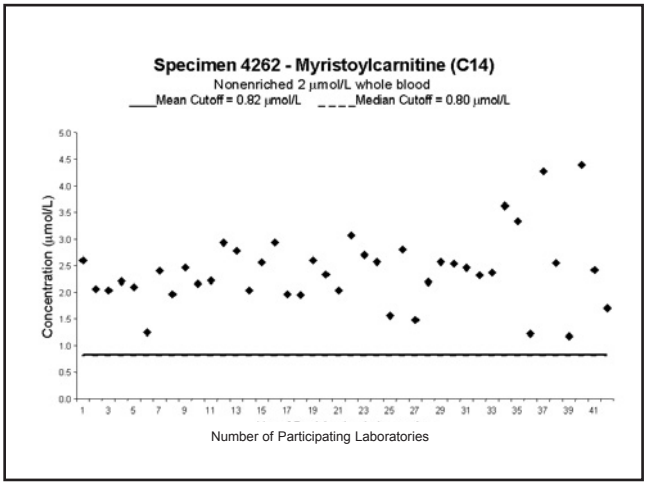

Figure 19b.

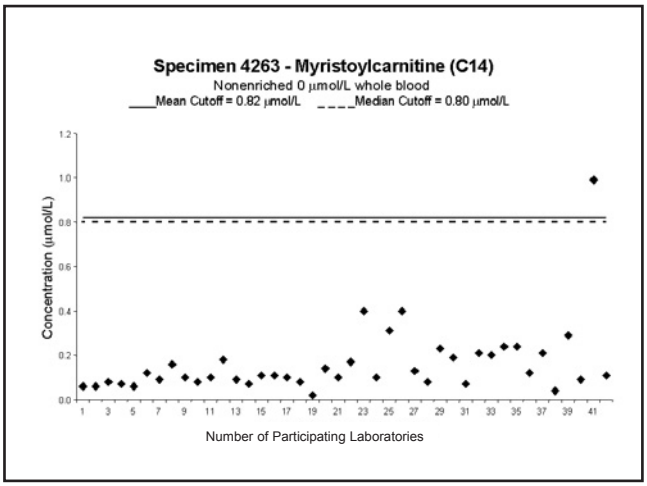

Figure 19c.

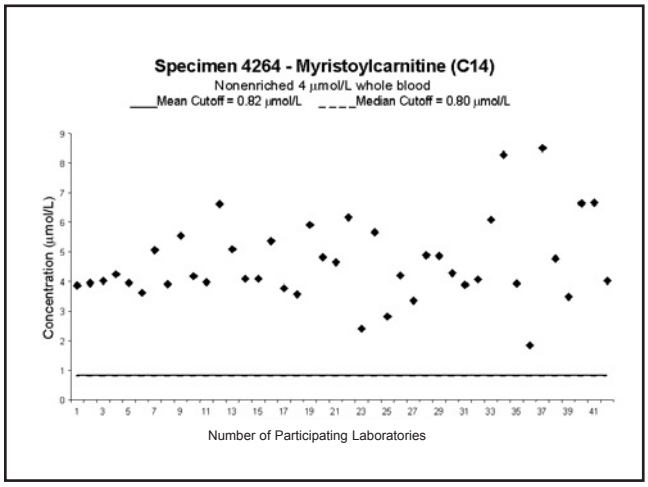

Figure 19d.

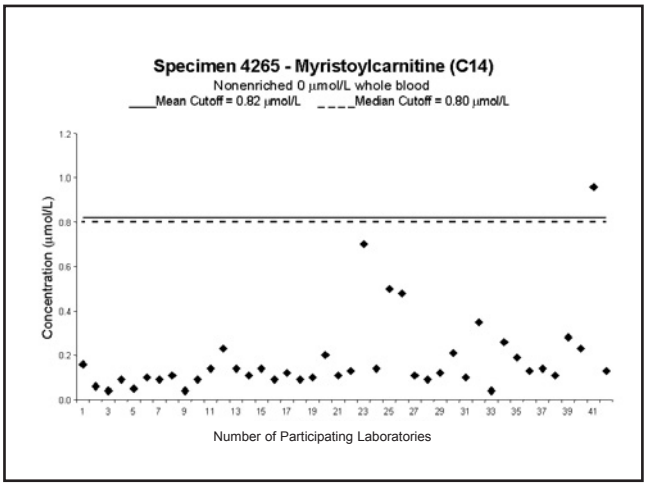

Figure 19e.

Figures 20a-20e. Participants' Results vs. Calculated Cutoff Mean and Median Values for Palmitoylcarnitine (C16)

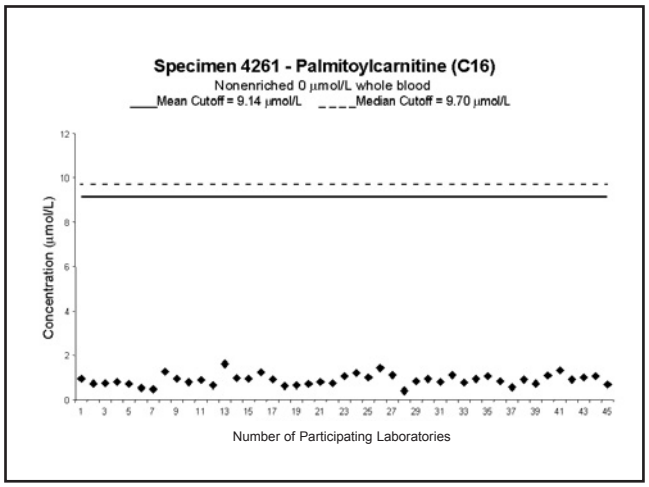

Figure 20a.

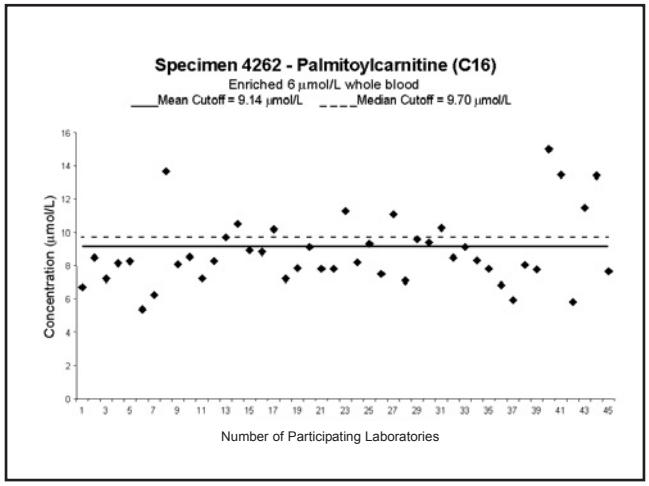

Figure 20b.

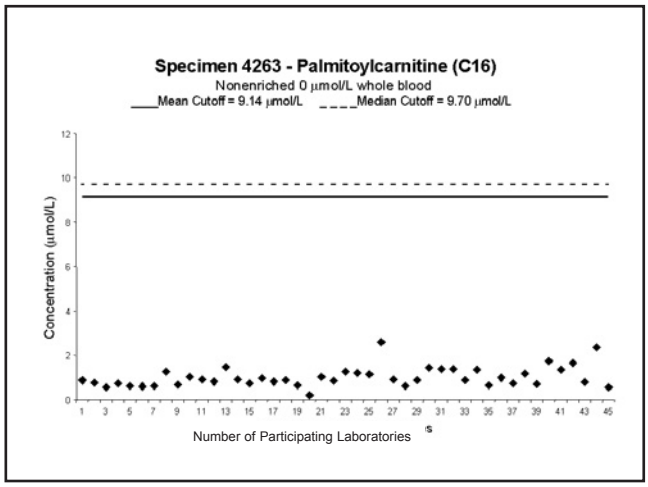

Figure 20c.

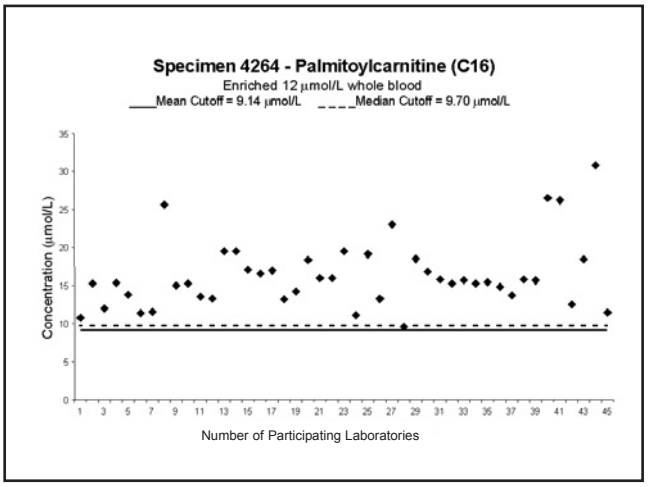

Figure 20d.

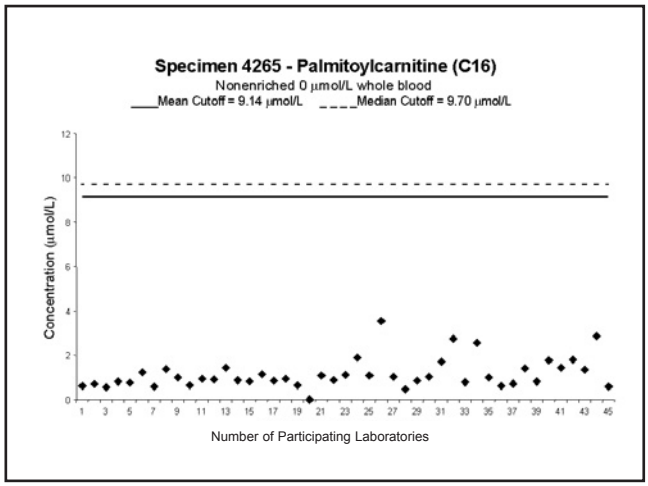

Figure 20e.

in Table 3. The percentage of error for each amino acid screen is shown separately for domestic and foreign participants. The rates for false-positive misclassifications are based on the number of distributed negative specimens, and the rates for false-negative misclassifications are based on the number of positive specimens. False positive rates of error range from 0 % - 1.9 % for domestic laboratories and for foreign laboratories, the rate was 0-4.3 %. Screening programs are designed to set cutoff values cautiously to avoid false-negative reports; however, this design may contribute to most of the false-positive misclassifications. Even though false-negative rates are expected to be zero, the range of errors went from 0 to 5.9 % among domestic laboratories, and 0 to 10.5 % among the foreign laboratories. The number of laboratories contributing to the percentage error is also included in the table.

The highest false negative rate of 10.5% occurred in the Citrulline results among the foreign laboratories. Citrulline is the newest amino acid to be added to our panel. With additional experience, error rates are expected to drop.

The National Center for Environmental Health's annual awards ceremony was held October 3, 2002. The Director's Award for Superior Mission Response - Science (Group) was presented to the "*Newborn Screening Quality Assurance Program for outstanding mission achievements as sole provider of comprehensive performance evaluation services and research to screening laboratories worldwide.*"

TABLE 3. 2002 Summary of Performance Evaluation Errors by Domestic and Foreign Laboratories in the Pilot Phase

Domestic	Positive Specimens Assayed (N)	False-Negative Errors (%)	Number of Error Labs	Negative Specimens Assayed (N)	False-Positive Errors (%)	Number of Error Labs
Phenylalanine Screen	60	1.7	1	40	0	
Leucine Screen	57	0		19	0	
Methionine Screen	60	1.7	1	20	0	
Tyrosince Screen	17	0		68	0	
Valine Screen	17	5.9	1	51	0	
Citrulline Screen	18	0		54	1.9	1

Foreign	Positive Specimens Assayed (N)	False-Negative Errors (%)	Number of Error Labs	Negative Specimens Assayed (N)	False-Positive Errors (%)	Number of Error Labs
Phenylalanine Screen	78	1.3	1	52	1.9	1
Leucine Screen	69	0		23	4.3	1
Methionine Screen	72	0		24	0	
Tyrosince Screen	26	0		104	1.9	2
Valine Screen	20	5.0	1	60	0	
Citrulline Screen	19	10.5	2	57	1.8	1

ACTIVITIES: PAST, PRESENT, AND FUTURE

- In 2002, MS/MS laboratory training sessions and diagnostic follow-up training sessions were held at the Duke University Medical Center, Research Triangle Park, North Carolina, and the Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas. The training sessions cosponsors' are the National Newborn Screening and Genetics Resource Center (NNSGRC), HRSA, CDC, and APHL. This training will continue to be offered in 2003 at no cost to state public health laboratories and their affiliates that are in the startup phase of bringing MS/MS into their laboratories for newborn testing. Laboratory classes will accommodate only five students per week, but the follow-up training sessions will accommodate much larger classes. The sessions will cover MS/MS interpretation as well as specific follow-up, confirmation, and long-term monitoring alternatives. The follow-up training session is scheduled for March 24-28, 2003, at Duke University Medical Center. The laboratory training sessions are scheduled for late summer and early fall 2003. For more information, please contact Brad Therrell, PhD, Director, NNSGRC, at 1912 W. Anderson Lane #210, Austin, Texas 78757, Phone: 512-454-6419, Fax: 512-454-6509, Web site: http://genes-r-us.uthscsa.edu.

- The NSQAP for tandem mass spectrometry is expanding. Markers of isovaleric academia (IVA) and glutaric acidemia type I (GA-1) will be added to the PT specimen panel for Quarter 2, 2003 distribution. This addition to the acylcarnitine panel will enhance our ability to assess the performance of laboratories screening for these disorders.

REFERENCES

1. Centers for Disease Control and Prevention. Using tandem mass spectrometry for metabolic disease screening among newborns: a report of a work group. MMWR 2001; 50(No. RR-3): 1-34.

2. Chace DH, Adam BW, Smith SJ, Alexander JR, Hillman SL, Hannon WH. Validation of accuracy-based amino acid reference materials in dried-blood spots by tandem mass spectrometry for newborn screening assays. Clin Chem 1999; 45:1269-77.

==========

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services or the Association of Public Health Laboratories.

This ***NEWBORN SCREENING QUALITY ASSURANCE PROGRAM*** report is an internal publication distributed to program participants and selected program colleagues. The laboratory quality assurance program is a project cosponsored by the **Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories.**

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GA 30341

Director
Julie Louise Gerberding, M.D., M.P.H.
Director
National Center for Environmental Health
Richard J. Jackson, M.D., M.P.H.
Director
Division of Laboratory Sciences
Eric J. Sampson, Ph.D.
Chief
Newborn Screening Branch
W. Harry Hannon, Ph.D.

Contributors:
Barbara W. Adam
Carol Bell
Paul Dantonio
Marie C. Earley, Ph.D.
Dimitri Fillos
F. Hugh Gardner
Sherri Hall
L. Omar Henderson, Ph.D.
Lisa Kalman, Ph.D.
Lixia Li, Ph.D.
Timothy Lim, Ph.D.
Elizabeth McCown
Joanne Mei, Ph.D.
Nancy Meredith
Jarad Schiffer
Anand Swamy, Ph.D.
Robert Vogt, Ph.D.

Production:
Connie Singleton
Sarah Brown
Sharon McNeely

ASSOCIATION OF PUBLIC HEALTH LABORATORIES
WASHINGTON, DC 20036-3320

President
David Mills, Ph.D.
Chairman, Newborn Screening and Genetics in Public Health Committee
Kenneth Pass, Ph.D.
Chairman, Newborn Screening Quality Assurance Subcommittee
John Sherwin, Ph.D.

INQUIRIES TO:

Nancy Meredith-Molloy, Editor ● Centers for Disease Control and Prevention (CDC)
Newborn Screening Quality Assurance Program ● Mailstop F-43
4770 Buford Highway, N.E. ● Atlanta, GA 30341-3724
Phone (770) 488-7897 ● FAX (770) 488-4255 ● E-mail: NMeredith@cdc.gov

NOTES

NOTES